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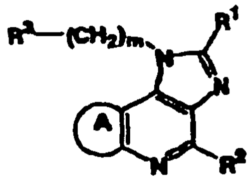
(54) 1H-IMIDAZOPYRIDINE DERIVATIVES

(57) 1H-Imidazopyridine derivatives represented by the following general formula or salts thereof:



wherein R^1 represents hydrogen atom, hydroxyl group, an alkyl group, a cycloalkyl group, styryl group, or an aryl group; R^2 represents hydrogen atom, an alkyl group, a halogen atom, hydroxyl group, amino group, a cyclic amino group, or phenoxy group; ring A represents a homocyclic or heterocyclic ring which may be substituted; R^3 represents a saturated nitrogen-containing heterocyclic group; and m represents an integer of from 0 to 3. The derivatives have excellent inhibitory actions against production of TNF or IL-1 and are extremely useful as preventive or therapeutic agents for diseases in which a cytokine is mediated.

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Description

Technical Field

[0001] The present invention relates to novel 1H-imidazopyridine derivatives or salts thereof which have a potent inhibitory action against production of tumor necrotizing factor (TNF) or interleukin-1 (IL-1) and are useful as medicaments for preventive or therapeutic treatment of diseases of humans and animals, in which a cytokine such as TNF, IL-1 is mediated, which include chronic inflammatory diseases (e.g., rheumatic arthritis, osteoarthritis, etc.), allergic rhinitis, atopic dermatitis, contact dermatitis, asthma, sepsis, septic shock, various autoimmune diseases [autoimmune hemic diseases (e g., hemolytic anemia, anaplastic anemia, idiopathic thrombocythemia, etc.), autoimmune intestinal diseases (e.g., ulcerative colitis, Crohn's disease, etc.), autoimmune corneitis (e.g., keratoconjunctivitis sicca, spring catarrh, etc.), endocrine ophthalmopathy, Graves disease, sarcoid granuloma, multiple sclerosis, systemic erythematodes, multiple chondritis, pachydermia, active chronic hepatitis, myasthenia gravis, psoriasis, interstitial pulmonary fibrosis and the like], diabetes, cancerous cachexia, HIV-infectious cachexia and the like.

Background Art

[0002] Some compounds having 1H-imidazoquinoline structure are known which are analogous to the compounds of the present invention. Journal of Medicinal Chemistry, Vol. 11, p. 87 (1968) discloses 1-(2-piperidinoethyl)-1H-imidazo[4,5-c]-quinoline, Japanese Patent Unexamined Publication (KOKAI) No. Sho 60-123488/1985 discloses 1-isobutyl-1H-imidazo[4,5-c]quinoline-4-amine (general name: imiquimod) as a compound having an antiviral action, and Hungarian Patent Publication No. 34479 (Patent No. 190109) discloses 1-(2-diethylaminoethyl)-1H-imidazo[4,5-c]quinoline as a compound having analgesic and anticonvulsant actions. However, 1H-imidazopyridine derivatives as those according to the present invention have never been known so far.

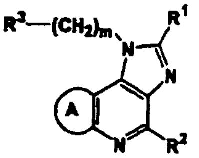
[C003] Moreover, the aforementioned imiquimod has been known to have an inducing action of a few kinds of cytokines such as interferon (IFN), TNF, IL-1 and the like, which is described in Journal of Interferon Research, Vol. 14, p. 81 (1994). However, 1H-imidazopyridine derivatives or 1H-imidazoquinoline derivatives having an inhibitory action against production of TNF or IL-1, which action is totally opposite to those taught by the aforementioned prior arts, have never been known so far.

Disclosure of the Invention

[0004] An object of the present invention is to provide novel compounds which have excellent inhibitory actions against production of cytokines such as TNF and IL-1 and the like are useful as medicaments.

[0005] The inventors of the present invention made intensive studies to achieve the object. As a result, they found novel 1H-imidazopyridine derivatives which have an excellent inhibitory action against production of TNF or IL-1 and achieved the present invention.

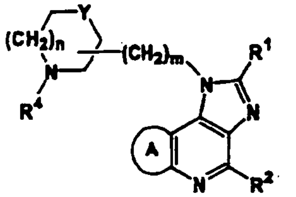
[0006] The present invention thus relates to novel 1H-imidazopyridine derivatives represented by the following general formula (I) or salts thereof:



(I)

wherein R^1 represents hydrogen atom, hydroxyl group, an alkyl group which may have one or more substituents, a cycloalkyl group which may be substituted, a styryl group which may be substituted, or an aryl group which may have one or more substituents; R^2 represents hydrogen atom, an alkyl group, a halogen atom, hydroxyl group, an amino group which may have one or two substituents, a cyclic amino group which may be substituted, or a phenoxy group which may be substituted; ring A represents a homocyclic or heterocyclic ring which may be substituted with one or more alkyl groups, alkoxyl groups, or halogen atoms; R^3 represents a saturated nitrogen-containing heterocyclic group which may be substituted; and m represents an integer of from 0 to 3; provided that, when R^3 represents unsubstituted piperidino group, at least one of R^1 and R^2 is not hydrogen atom.

[0007] According to the second embodiment of the present invention, there are provided novel 1H-imidazopyridine derivatives represented by the following general formula (II) or salts thereof:



(II)

wherein R^1, R^2, ring A and m have the same meanings as those defined above; R^4 represents hydrogen atom, an alkyl group, benzyl group, triphenylmethyl group, an alkanoyl group which may be substituted, an alkoxycarbonyl group, benzyloxycarbonyl group, a thiocarbamoyl group which may be substituted, an alkanesulfonyl group, a benzenesulfonyl group which may be substituted, or amidino group; Y represents methylene group, oxygen atom, sulfur atom, nitrogen atom, a group represented by NH, or a single bond; and n represents an integer of from 0 to 2.

[0008] According to the third embodiment of the present invention, there are provided, among the compounds represented by the aforementioned general formulas (I) and (II), the compounds wherein ring A is a benzene ring or a thiophene ring, or the salts thereof.

[0009] According to another aspect, there is provided a medicament which comprises as an active ingredient the compound represented by the aforementioned general formula (I) or (II), or a pharmacologically acceptable salt thereof. The medicament is useful for preventive or therapeutic treatment of diseases of mammals including humans, in which a cytokine such as TNF, IL-1 is mediated, which include chronic inflammatory diseases (e.g., rheumatic arthritis, osteoarthritis, etc.), allergic rhinitis, atopic dermatitis, contact dermatitis, asthma, sepsis, septic shock, various autoimmune diseases [autoimmune hemic diseases (e.g., hemolytic anemia, anaplastic anemia, idiopathic thrombocythemia, etc.), autoimmune intestinal diseases (e.g., ulcerative colitis, Crohn's disease, etc.), autoimmune corneitis (e.g., keratoconjunctivitis sicca, spring catarrh, etc.), endocrine ophthalmopathy, Graves disease, sarcoid granuloma, multiple sclerosis, systemic erythematodes, multiple chondritis, pachydermia, active chronic hepatitis, myasthenia gravis, psoriasis, interstitial pulmonary fibrosis and the like], diabetes, cancerous cachexia, HIV-infectious cachexia and the like.

[0010] According to a further aspect, there are provided a use of the compound represented by the aforementioned general formula (I) or (II), or a pharmacologically acceptable salt thereof for the manufacture of the aforementioned medicament; and a method for the preventive or therapeutic treatment of diseases in which a cytokine such as TNF, IL-1 is mediated, which comprises the step of administering a preventively or therapeutically effective amount of the compound represented by the aforementioned general formula (I) or (II), or a pharmacologically acceptable salt thereof to a mammal including a human. In addition, the present invention provides an inhibitor against production of tumor necrotizing factor (TNF) or interleukin-1 (IL-1) which comprises as an active ingredient the compound represented by the aforementioned general formula (I) or (II), or a pharmacologically acceptable salt thereof.

Best Mode for Carrying Out the Invention

[0011] Specific explanations of the compounds of the aforementioned general formulas (I) and (II) of the present invention will be given below. The compounds represented by the aforementioned general formula (II) are characterized in that they have a specific saturated nitrogen-containing heterocyclic group which may have specific substituents as R^3 among the compounds represented by the aforementioned general formula (I). However, the scope of the present invention is not limited to the compounds represented by the aforementioned general formula (II), and it should be understood that any compounds having as R^3 a saturated nitrogen-containing heterocyclic group which may be substituted fall within the scope of the present invention.

[0012] In the aforementioned general formulas (I) and (II), examples of the alkyl group represented by R^1, R^2 or R^4 include, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-pentyl group, isopentyl group, neopentyl group, n-hexyl group and the like.

[0013] Examples of the cycloalkyl group represented by R^1 include, for example, cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group and the like. Examples of the aryl group represented by R^1 include, for example, phenyl group, 2-pyridyl group, 3-pyridyl group, 4-pyridyl group, 3-pyridazinyl group, 4-pyridazinyl group, 2-pyrimidinyl group, 4-pyrimidinyl group, 5-pyrimidinyl group, pyrazinyl group, 2-furyl group, 3-furyl group, 2-thienyl group, 3-thienyl group, 1-pyrrolyl group, 2-pyrrolyl group, 3-pyrrolyl group, 1-imidazolyl group, 2-imidazolyl group, 4-imidazolyl group, 1-pyrazolyl group, 3-pyrazolyl group, 4-pyrazolyl group, 5-pyrazolyl group, 2-oxazolyl group, 4-oxazolyl group, 3-isoxazolyl group, 4-isoxazolyl group, 5-isoxazolyl group, 2-thiazolyl group, 4-thiazolyl group, 5-thiazolyl group, 3-isothiazolyl group, 4-isothiazolyl group, 5-isothiazolyl group, 1,2,3-triazol-1-yl group, 1,2,3-triazol-4-yl group, 1,2,3-triazol-5-yl group, 1,2,4-triazol-1-yl group, 1,2,4-triazol-3-yl group, 1,2,4-triazol-5-yl group, 1-tetrazolyl group, 5-tetrazolyl group, 1,2,5-thiadiazol-3-yl group, 1-indolyl group, 2-indolyl group, 3-indolyl group and the like

[0014] Examples of the halogen atom represented by R^2 include, for example, fluorine atom, chlorine atom, bromine atom, and iodine atom. Examples of the amino group which may have one or two substituents that is represented by R^2 include, for example, amino group, methylamino group, ethylamino group, n-propylamino group, isopropylamino group, cyclopropylamino group, cyclobutylamino group, cyclopentylamino group, cyclohexylamino group, dimethylamino group, diethylamino group, anilino group, pyridylamino group, 4-pyridylmethylamino group, benzylamino group, p-methoxybenzylamino group, dibenzylamino group and the like. Examples of the cyclic amino group represented by R^2 include, for example, 1-aziridinyl group, 1-azetidinyl group, 1-pyrrolidinyl group, piperidino group, 1-piperazinyl group, hexahydro-1H-azepin-1-yl group, hexahydro-1H-1,4-diazepin-1-yl group, morpholino group, 4-thiomorpholinyl group and the like.

[0015] Examples of the homocyclic or heterocyclic ring represented by ring A in the aforementioned general formulas (I) and (II) include, for example, benzene ring, cyclopentene ring, cyclohexene ring, cycloheptene ring, cyclooctene ring, cycloheptadiene ring, thiophene ring, furan ring, pyridine ring, pyrazine ring, pyrrole ring, thiazole ring, oxazole ring, azepine ring and the like. Examples of the alkyl group which may be substituted on the homocyclic or heterocyclic ring include, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-pentyl group, isopentyl group, neopentyl group, n-hexyl group and the like. Examples of the alkoxyl group which may be substituted on the said ring include, for example, methoxy group, ethoxy group, n-propoxy group, isopropoxy group, n-butoxy group, isobutoxy group, sec-butoxy group, tert-butoxy group, n-pentyloxy group, isopentyloxy group, neopentyloxy group, n-hexyloxy group and the like. Examples of the halogen atom which may be substituted on the said ring include, for example, fluorine atom, chlorine atom, bromine atom, and iodine atom. The number and kind of these substituents are not particularly limited, and when two or more substituents exist, they may be the same or different.

[0016] In the aforementioned general formula (I), the saturated nitrogen-containing heterocyclic group represented by R^3 means a saturated nitrogen-containing heterocyclic group which has one or more nitrogen atoms as ring-constituting atom(s), and which may further have one or more oxygen atoms or sulfur atoms as ring-constituting atoms. Examples include 1-aziridinyl group, 2-aziridinyl group, 1-azetidinyl group, 2-azetidinyl group, 3-azetidinyl group, 1-pyrrolidinyl group, 2-pyrrolidinyl group, 3-pyrrolidinyl group, pyrazolidinyl group, imidazolidinyl group, piperidino group, 2-piperidyl group, 3-piperidyl group, 4-piperidyl group, 1-piperazinyl group, 2-piperazinyl group, hexahydro-1H-azepin-1-yl group, hexahydro-1H-azepin-2-yl group, hexahydro-1H-azepin-3-yl group, hexahydro-1H-azepin-4-yl group, hexahydro-1H-1,4-diazepin-1-yl group, hexahydro-1H-1,4-diazepin-2-yl group, hexahydro-1H-1,4-diazepin-5-yl group, hexahydro-1H-1,4-diazepin-6-yl group, 2-morpholinyl group, 3-morpholinyl group, morpholino group, 2-thiomorpholinyl group, 3-thiomorpholinyl group, 4-thiomorpholinyl group, 3-isoxazolidinyl group, 3-isothiazolidinyl group, 1,2,3-triazolidin-4-yl group, 1,2,4-triazolidin-3-yl group, 1,2,5-thiadiazolin-3-yl group and the like, and preferred groups include, for example, 3-piperidyl group, 4-piperidyl group, 1-piperazinyl group, 2-piperazinyl group, 3-pyrrolidinyl group, 2-azetidinyl group, 3-azetidinyl group, 2-morpholinyl group, 2-thiomorpholinyl group and the like.

[0017] In the aforementioned general formula (II), examples of the alkanoyl group which may be substituted that is represented by R^4 include, for example, formyl group, acetyl group, propionyl group, n-butyryl group, isobutyryl group, valeryl group, isovaleryl group, pivaloyl group, fluoroacetyl group, difluoroacetyl group, trifluoroacetyl group, chloroacetyl group, dichloroacetyl group, trichloroacetyl group and the like. Examples of the alkoxycarbonyl group represented by R^4 include, for example, methoxycarbonyl group, ethoxycarbonyl group, n-propoxycarbonyl group, isopropoxycarbonyl group, n-butoxycarbonyl group, isobutoxycarbonyl group, sec-butoxycarbonyl group, tert-butoxycarbonyl group, n-pentyloxycarbonyl group, n-hexyloxycarbonyl group and the like. Examples of the thiocarbamoyl group which may be substituted that is represented by R^4 include, for example, thiocarbamoyl group, methylthiocarbamoyl group, ethylthiocarbamoyl group, n-propylthiocarbamoyl group, isopropylthiocarbamoyl group, n-butylthiocarbamoyl group, isobutylthiocarbamoyl group, sec-butylthiocarbamoyl group, tert-butylthiocarbamoyl group and the like. Examples of the alkanesulfonyl group represented by R^4 include, for example, methanesulfonyl group, ethanesulfonyl group, n-propanesulfonyl group, n-butanesulfonyl group and the like.

[0018] In the present specification, with respect to the substituting/binding position of the terms "the aryl group", "the homocyclic or heterocyclic ring" and "saturated nitrogen-containing heterocyclic group", the terms herein used encompass any groups in their meanings which may substitute/bind at any position on a substitutable/bondable element among ring-constituting atoms, so long as the substituting/binding position is not particularly limited, as some examples are shown above.

[0019] In the aforementioned general formulas (I) and (II) of the present invention, when certain functional groups are referred to as "which may be substituted" or "which may have substitutents," the substituent may be any group so long as it can substitute on the functional groups. The number and kind of the substituent are not particularly limited, and when two or more substituents exist, they may be the same or different. Examples include halogen atoms such as fluorine atom, chlorine atom, and bromine atom; hydroxyl group; alkyl groups such as methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-pentyl group, isopentyl group, neopentyl group, and n-hexyl group; trifluoromethyl group; aryl groups such as phenyl group, naphthyl group, and pyridyl group; alkoxyl groups such as methoxy group, ethoxy group, n-propoxy group, isopropoxy group, n-butoxy group, isobutoxy group, sec-butoxy group, and tert-butoxy group; aryloxy groups such as phenoxy group; amino groups which may be substituted such as amino group, methylamino group, ethylamino group, n-propylamino group, isopropylamino group, cyclopropylamino group, cyclobutylamino group, cyclopentylamino group, cyclohexylamino group, dimethylamino group, diethylamino group, anilino group, pyridylamino group, benzylamino group, dibenzylamino group, acetylamino group, trifluoroacetylamino group, tert-butoxycarbonylamino group, benzyloxycarbonylamino group, benzhydrylamino group, and triphenylmethylamino group; formyl group; alkanoyl groups such as acetyl group, propionyl group, n-butyryl group, isobutyryl group, valeryl group, isovaleryl group, pivaloyl group, fluoroacetyl group, difluoroacetyl group, trifluoroacetyl group, chloroacetyl group, dichloroacetyl group, and trichloroacetyl group; alkoxycarbonyl groups such as methoxycarbonyl group, ethoxycarbonyl group, n-propoxycarbonyl group, isopropoxycarbonyl group, n-butoxycarbonyl group, isobutoxycarbonyl group, sec-butoxycarbonyl group, tert-butoxycarbonyl group, n-pentyloxycarbonyl group, and n-hexyloxycarbonyl group; benzyloxycarbonyl group; carbamoyl group; alkylcarbamoyl groups such as methylcarbamoyl group, ethylcarbamoyl group, n-propylcarbamoyl group, isopropylcarbamoyl group, n-butylcarbamoyl group, isobutylcarbamoyl group, sec-butylcarbamoyl group, and tert-butylcarbamoyl group; thiocarbamoyl group; alkylthiocarbamoyl groups such as methylthiocarbamoyl group, ethylthiocarbamoyl group, n-propylthiocarbamoyl group, isopropylthiocarbamoyl group, n-butylthiocarbamoyl group, isobutylthiocarbamoyl group, sec-butylthiocarbamoyl group, and tert-butylthiocarbamoyl group; amidino group; alkylthio groups such as methylthio group; alkanesulfinyl groups such as methanesulfinyl group; alkanesulfonyl groups such as methanesulfonyl group, ethanesulfonyl group, n-propanesulfonyl group, and n-butanesulfonyl group; arylsulfonyl groups such as p-toluenesulfonyl group, p-methoxybenzenesulfonyl group, and p-fluorobenzenesulfonyl group; aralkyl groups such as benzyl group, naphthyl group, pyridylmethyl group, furfuryl group, and triphenylmethyl group; nitro group; cyano group; sulfamoyl group; oxo group; hydroxyimino group; alkoxyimino groups such as methoxyimino group, ethoxyimino group, n-propoxyimino group, and isopropoxyimino group; ethylenedioxy group and the like.

[0020] The compounds represented by the aforementioned general formulas (I) and (II) of the present invention can be converted into salts, preferably, pharmacologically acceptable salts, if desired; or free bases can be generated from the resulting salts.

[0021] Examples of the salts, preferably, the pharmacologically acceptable salts, of the compounds represented by the aforementioned general formulas (I) and (II) of the present invention include acid-addition salts, for example, salts with mineral acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid, sulfuric acid, and phosphoric acid; and salts with organic acids such as acetic acid, propionic acid, butyric acid, formic acid, valeric acid, maleic acid, fumaric acid, citric acid, oxalic acid, malic acid, succinic acid, lactic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, mandelic acid, 10-camphorsulfonic acid, tartaric acid, stearic acid, gluconic acid, nicotinic acid, trifluoroacetic acid, and benzoic acid.

[0022] Among the compounds represented by the aforementioned general formulas (I) and (II) of the present invention, optical isomers may exist for compounds having asymmetric carbons. These optical active compounds and mixtures thereof fall within the scope of the present invention.

[0023] The compounds represented by the aforementioned general formulas (I) and (II) or the salts thereof according to the present invention can exist as any crystalline form depending on manufacturing conditions, or exist as any hydrate or solvate. These crystalline forms, hydrates or solvates, and mixtures thereof fall within the scope of the present invention.

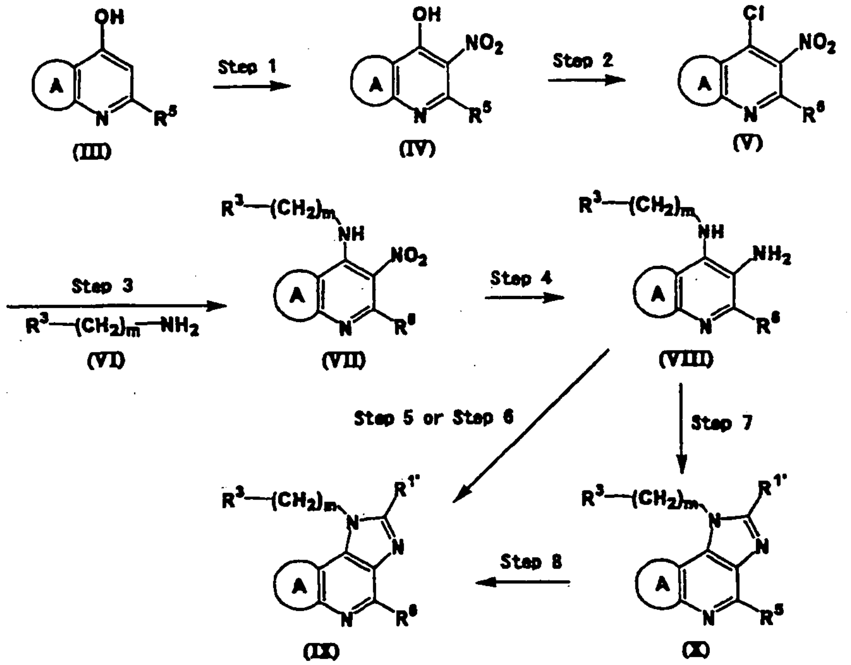
[0024] Preferred compounds of the present invention include, for example, the following compounds and salts thereof; however, the present invention is not limited to these examples:

(1) 4-chloro-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(2) 4,8-dichloro-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(3) 4-chloro-8-methyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(4) 4-chloro-8-methoxy-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(5) 4-chloro-2-phenyl-1-[2 -(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(6) 4,8-dichloro-2-phenyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(7) 4-chloro-8-methyl-2-phenyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5 -c]quinoline;
(8) 4-chloro-8-methoxy-2-phenyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(9) 4-chloro-1-[2-(4-piperidyl)ethyl]-2-trifluoromethyl-1H-imidazo[4,5-c]quinoline;
(10) 4,8-dichloro-1-[2-(4-piperidyl)ethyl]-2 -trifluoromethyl-1H-imidazo[4,5-c]quinoline;
(11) 4-chloro-8-methyl-1-[2-(4-piperidyl)ethyl]-2-trifluoromethyl-1H-imidazo[4,5-c]quinoline;
(12) 4-chloro-8-methoxy-1-[2-(4-piperidyl)ethyl]-2-trifluoromethyl-1H-imidazo[4,5-c]quinoline;

(13) 4-chloro-2-(4-methylphenyl)-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(14) 4-chloro-2-(4-methoxyphenyl)-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(15) 4-chloro-2-(4-fluorophenyl)-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(16) 4-chloro-1-[2 -(4-piperidyl)ethyl]-2-(4-trifluoromethylphenyl)-1H-imidazo[4,5-c]quinoline;
(17) 4-chloro-2-(2-furyl)-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(18) 4-chloro-1-[2-(4-piperidyl)ethyl]-2-(2-thienyl)-1H-imidazo[4,5-c]quinoline;
(19) 4-chloro-2-(2-imidazolyl)-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(20) 4-chloro-1-[2-(4-piperidyl)ethyl]-2-(2-thiazolyl)-1H-imidazo[4,5-c]quinoline;
(21) 4-chloro-2-(5-methyl-2-thienyl)-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(22) 4-chloro-1-[2-(4-piperidyl)ethyl]-2-(2-pyrrolyl)-1H-imidazo[4,5-c]quinoline;
(23) 4-methyl-2-phenyl-1-[2 -(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(24) 2-(4-fluorophenyl)-4-methyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(25) 4-methyl-1-[2-(4-piperidyl)ethyl]-2-(4-trifluoromethylphenyl)-1H-imidazo[4,5-c]quinoline;
(26) 2-(2-furyl)-4-methyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(27) 4-methyl-1-[2-(4-piperidyl)ethyl]-2-(2-thienyl)-1H-imidazo[4,5-c]quinoline;
(28) 2-(2-imidazolyl)-4-methyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(29) 4-methyl-1-[2-(4-piperidyl)ethyl]-2-(2-thiazolyl)-1H-imidazo[4,5-c]quinoline;
(30) 4-methyl-2-(3-methyl-2-thienyl)-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(31) 4-methyl-2-(5-methyl-2-thienyl)-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(32) 4-methyl-1-[2-(4-piperidyl)ethyl]-2-(2-pyrrolyl)-1H-imidazo[4,5-c]quinoline;
(33) 4-methyl-2-(1-methyl-2-pyrrolyl)-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(34) 4-chloro-6,7,8,9-tetrahydro-2-phenyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(35) 4-chloro-6,7-dihydro-2-phenyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[5,4-d]cyclopenta[b]pyridine;
(36) 4-chloro-2-phenyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[5,4-d]thieno-[3,2-b]pyridine;
(37) 4-chloro-2-phenyl-1-[2-(3-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(38) 4-chloro-1-[2-(2-morpholinyl)ethyl]-2-phenyl-1H-imidazo[4,5-c]quinoline;
(39) 4-chloro-2-phenyl-1-[2-(1-piperazinyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(40) 4,6,7,8,9-pentachloro-2-ethoxymethyl-1-[2-(4-thiomorpholinyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(41) 4-chloro-6,7,8,9-tetrahydro-2-hydroxymethyl-1-[2-(1-piperazinyl)ethyl]-1H-imidazo[5,4-d]cyclohepta[b]pyridine; and
(42) 4-chloro-2-(3-methyl-2-thienyl)-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline.

[0025] The novel 1H-imidazopyridine derivatives represented by the aforementioned general formula (I) or (II) according to the present invention can be prepared by various methods; however, the preparation methods of the compounds of the present invention are not limited thereto. In the following preparation methods, specific explanations for the compounds represented by the aforementioned general formula (I) will be given, and it is obvious that these preparation methods include the compounds represented by the aforementioned general formula (II).

[0026] As the first synthetic method of the compounds of the present invention, the following synthetic method can be used in accordance with the method disclosed in Japanese Patent Unexamined Publication (KOKAI) No. Hei 3-206078/1991 or Tetrahedron, Vol. 51, p. 5813 (1995):



wherein R^5 represents hydroxyl group or an alkyl group; R^6 represents chlorine atom or an alkyl group; $R^{1'}$ has the same meaning as that defined for R^1 (except for hydroxyl group); and R^3, m and ring A have the same meanings as those defined above.

[0027] In Step 1, the compound of the general formula (IV) can be obtained by allowing the compound represented by the general formula (III) to react with a nitrating agent such as concentrated nitric acid and fuming nitric acid in the presence or absence of acetic acid, sulfuric acid or the like at a temperature ranging from 0°C to 200°C.

[0028] In Step 2, the compound of the general formula (V) can be obtained by allowing the compound of the general formula (IV) to react with an appropriate chlorinating agent, for example, phosphorus oxychloride, thionyl chloride, phosgene, oxalyl chloride, phosphorus pentachloride or the like, in the presence or absence of a solvent such as toluene at a temperature ranging from 0°C to 200°C.

[0029] In Step 3, the compound of the general formula (VII) can be obtained by reacting the amine represented by the general formula (VI) with the compound of the general formula (V) in a solvent such as N,N-dimethylformamide and toluene in the presence or absence of a base such as triethylamine and potassium carbonate at a temperature ranging from -10°C to the reflux temperature of a solvent.

[0030] In Step 4, the compound of the general formula (VIII) can be obtained by reducing the nitro group in the compound of the general formula (VII) according to an appropriate reducing method, for example, catalytic reduction using a metal catalyst such as platinum, Raney nickel, and palladium/carbon; reduction using nickel chloride and sodium borohydride; reduction using iron powder and hydrochloric acid and the like.

[0031] The reduction can be carried out in a solvent such as water, methanol, ethanol, and tetrahydrofuran, as well as a mixed solvent thereof, at a temperature ranging from 0°C to the reflux temperature of the solvent.

[0032] In Step 5, the compound of the general formula (IX) can be obtained by reacting the compound of the general formula (VIII) with a compound represented by the following general formula (XI), (XII) or (XIII):

$$R^{1'}C(OR)_3 \qquad (XI)$$

$$R^{1'}COX \qquad (XII)$$

$$(R^{1'}CO)_2O \qquad \text{(XIII)}$$

wherein R represents a lower alkyl group; X represents a halogen atom; $R^{1'}$ has the same meaning as that defined for R^1 (except for hydroxyl group),
in the presence or absence of a basic catalyst such as triethylamine, or an acid catalyst such as hydrochloric acid and p-toluenesulfonic acid, in the presence or absence of a solvent such as N,N-dimethylformamide, tetrahydrofuran, acetonitrile, xylene and toluene, at a temperature ranging from 0°C to 200°C.

[0033] In Step 6, as a method in place of Step 5, the compound of the general formula (IX) can be obtained by reacting the compound of the general formula (VIII) with a compound represented by the following general formula (XIV):

$$R^{1'}CHO \qquad \text{(XIV)}$$

wherein $R^{1'}$ has the same meaning as that defined for R^1 (except for hydroxyl group), in the presence of2,3-dichloro-5,6-dicyano-1,4-benzoquinone in a solvent such as acetonitrile, 1,4-dioxane and tetrahydrofuran at a temperature ranging from 0°C to the reflux temperature of the solvent.

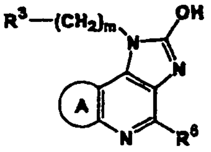
[0034] In Step 7, as a method in place of Step 5 or 6, the compound of the general formula (X) can be obtained by reacting the compound of the aforementioned general formula (VIII) with a compound represented by the following general formula (XV):

$$R^{1'}COOH \qquad \text{(XV)}$$

wherein $R^{1'}$ has the same meaning as that defined for R^1 (except for hydroxyl group), in the presence or absence of an acid catalyst such as hydrochloric acid and sulfuric acid, in the presence or absence of a solvent such as N,N-dimethylformamide and toluene, at a temperature ranging from 0°C to 200°C. Moreover, when R^5 represents hydroxyl group in the general formula (X), the compound of the general formula (IX) can be obtained by carrying out chlorination in Step 8.

[0035] The chlorination is carried out by protecting the compound of the general formula (X), if desired, at the nitrogen atom not bound to the $(CH_2)_m$ group, that is adjacent to the saturated nitrogen-containing heterocyclic group represented by R^3, with a protecting group such as alkanoyl groups in a conventional manner, then reacting with an appropriate chlorinating agent, for example, phosphorus oxychloride, thionyl chloride, phosgene, oxalyl chloride, phosphorus pentachloride or the like in the presence or absence of a solvent such as toluene at a temperature ranging from 0°C to 200°C, and further deprotecting in a conventional manner, if desired, to obtain the compound of the general formula (IX) wherein R^6 is chlorine atom.

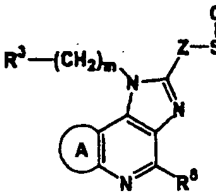
[0036] In the second synthetic method of the compounds of the present invention, the compound of the general formula (XVI):



(XVI)

wherein R^3, R^6, m and ring A have the same meanings as those defined above,
can be obtained by allowing the compound of the general formula (VIII) to react together with triphosgene in the presence of a base such as triethylamine and potassium carbonate in a solvent such as 1,2-dichloroethane, 1,4-dioxane, tetrahydrofuran, N,N-dimethylformamide and toluene at a temperature ranging from 0°C to the reflux temperature of a solvent.

[0037] In the third synthetic method of the compounds of the present invention, the compound of the general formula (XVII):



(XVII)

wherein Z represents an aromatic ring; the symbol "a" represents an integer of 1 or 2; and R^3, R^6, m and ring A have the same meanings as those defined above, can be obtained by carrying out suitable oxidation of the compound of the general formula (IX) which has an aryl group substituted with methylthio group as $R^{1'}$, after protecting, if desired, the nitrogen atom not bound to the $(CH_2)_m$ group, that is adjacent to the saturated nitrogen-containing heterocyclic group represented by R^3, with a protecting group such as alkanoyl groups in a conventional manner, and further deprotecting in a conventional manner, if desired.

[0038] The oxidation can be carried out in various manners according to the desired product. More specifically, the preparation can be made, when the symbol "a" represents an integer of 1, by reacting with an oxidizing agent, for example, chromic acid, hydrogen peroxide, m-chloroperbenzoic acid, sodium periodate, potassium periodate or the like, or when the symbol "a" represents an integer of 2, with an oxidizing agent, for example, chromic acid, hydrogen peroxide, m-chloroperbenzoic acid, osmium tetraoxide, ruthenium tetraoxide or the like, in a solvent such as tetrahydrofuran, 1,4-dioxane, 1,2-dichloroethane, methanol, acetone, and water, as well as a mixed solvent thereof, at a temperature ranging from 0°C to the reflux temperature of a solvent.

[0039] In the forth synthetic method of the compounds of the present invention, the compound of the general formula (I) wherein R^2 is hydroxyl group can be obtained by allowing a compound of the general formula (I) wherein R^2 is chlorine atom to react with water and an appropriate acid or base in a solvent at a temperature ranging from 0°C to the reflux temperature of a solvent. Examples of the appropriate acid include, for example, organic acids such as formic acid, acetic acid, and trifluoroacetic acid, and mineral acids such as hydrochloric acid, sulfuric acid, and hydrobromic acid. Examples of the appropriate base include, for example, hydroxides, carbonates and hydrogencarbonates of alkali metal such as sodium and potassium and of alkaline-earth metal such as magnesium and calcium and the like. Examples of the solvent include, for example, alcohols such as methanol, ethanol and n-propanol, N,N-dimethylformamide, 1,4-dioxane, tetrahydrofuran and the like, and water-containing solvents thereof.

[0040] In the fifth synthetic method of the compounds of the present invention, the compound of the general formula (I) wherein R^2 is fluorine atom, bromine atom or iodine atom and R^1 is $R^{1'}$ can be obtained by allowing a compound which is obtained by reacting the compound of the general formula (I) wherein R^2 is chlorine atom and R^1 is $R^{1'}$ or wherein R^2 is hydroxyl group and R^1 is $R^{1'}$ with trifluoromethanesulfonic anhydride, methanesulfonyl chloride or p-toluenesulfonyl chloride to react with a metal halide (e.g., potassium fluoride, sodium fluoride, lithium fluoride, potassium bromide, sodium bromide, potassium iodide, sodium iodide, etc.) in an aprotic solvent such as dimethylsulfoxide, N, N-dimethylformamide, and acetonitrile in the presence or absence of a phase-transfer catalyst such as tetraphenylphosphonium bromide, hexadecyltributylphosphonium bromide, and 18-crown-6 at a temperature ranging from 0°C to the reflux temperature of a solvent.

[0041] In the sixth synthetic method of the compounds of the present invention, the compound of the general formula (I), wherein R^3 is a saturated nitrogen-containing heterocyclic group of which the nitrogen atom that is not bound to the adjacent $(CH_2)_m$ group is deprotected, can be obtained by subjecting the compound of the general formula (I), wherein R^3 is a saturated nitrogen-containing heterocyclic group having a protecting group such as alkanoyl groups, alkoxycarbonyl groups, benzyl group and trifluoromethyl group on the nitrogen atom which is not bound to the adjacent $(CH_2)_m$ group, to deprotection with an acid or alkali, or to catalytic reduction with a metal catalyst, according to the type of the protecting group of the nitrogen atom.

[0042] The deprotection by using an acid or alkali can be carried out with an appropriate acid or base in the presence or absence of a cation scavenger such as anisole and thioanisole in a solvent. Examples of the solvent used include, for example, ethyl acetate, methylene chloride, 1,2-dichloroethane, 1,4-dioxane, methanol, ethanol, n-propanol, N,N-dimethylformamide, tetrahydrofuran, and water, as well as a mixed solvent thereof. Examples of the acid used include, for example, hydrochloric acid, an ethyl acetate solution of hydrogen chloride, an ethanolic solution of hydrogen chloride, sulfuric acid, hydrobromic acid, trifluoroacetic acid, methanesulfonic acid, p-toluenesulfonic acid, formic acid, acetic acid and the like. Examples of the base include, for example, hydroxides, carbonates and hydrogencarbonates of alkali metal such as sodium and potassium, and of alkaline-earth metal such as magnesium and calcium and the like. The reaction can be carried out at a temperature ranging from 0°C to the reflux temperature of a solvent.

[0043] The catalytic reduction can be carried out by using an appropriate metal catalyst such as platinum, palladium/

carbon, Raney nickel, Pearlman's reagent in water, an alcohol such as methanol, ethanol and n-propanol, and acetic acid, as well as a mixed solvent thereof in the presence or absence of an acid such as hydrochloric acid at a temperature ranging from room temperature to the reflux temperature of the solvent under a pressure ranging from normal pressure to 200 kg/cm^2

[0044] In the seventh synthetic method of the compounds of the present invention, the compound of the general formula (I) wherein R^2 is phenoxy group which may be substituted can be obtained by reacting the compound of the general formula (I) wherein R^2 is chlorine atom with a phenol derivative which may be substituted in the presence of a base such as sodium hydroxide and potassium hydroxide in the presence or absence of a solvent such as N,N-dimethylformamide and toluene at a temperature ranging from 0°C to 200°C.

[0045] In the eighth synthetic method of the compounds of the present invention, the compound of the general formula (I) wherein R^2 is amino group can be obtained by subjecting the compound of the general formula (I) wherein R^2 is phenoxy group which may be substituted, that is obtained by the seventh synthetic method, to reaction together with ammonium acetate in the presence or absence of a solvent such as N,N-dimethylformamide and toluene at a temperature ranging from 0°C to 200°C.

[0046] In the ninth synthetic method of the compounds of the present invention, the compound of the general formula (I) wherein R^2 is amino group which may have one or two substituents or a cyclic amino group which may be substituted can be obtained by subjecting the compound of the general formula (I) wherein R^2 is chlorine atom to reaction together with an amine derivative which may have one or two substituents or a cyclic amine derivative which may be substituted in the presence or absence of a base such as triethylamine, potassium carbonate and sodium hydride in the presence or absence of a solvent such as water, alcohols including methanol, ethanol and n-propanol, methylene chloride, 1,2-dichlroethane, N,N-dimethylformamide, 1,4-dioxane, tetrahydrofuran and toluene at a temperature ranging from 0°C to 200°C under normal pressure or a pressurized condition.

[0047] In the tenth synthetic method of the compounds of the present invention, the compound of the general formula (I) wherein R^2 is amino group can be obtained by subjecting the compound of the general formula (I) wherein R^2 is benzylamino group, dibenzylamino group, or p-methoxybenzylamino group, which is obtained in the ninth synthetic method, to catalytic reduction by using an appropriate metal catalyst, or by subjecting the compound of the general formula (I) wherein R^2 is p-methoxybenzylamino group to deprotection using an acid.

[0048] The catalytic reduction can be carried out with a metal catalyst such as palladium/carbon and Pearlman's reagent in a solvent such as alcohols including methanol and ethanol, and water, as well as a mixed solvent thereof at a temperature ranging from room temperature to the reflux temperature of a solvent in the presence or absence of an acid such as hydrochloric acid, acetic acid and formic acid, ammonium formate, cyclohexene, and cyclohexadiene under a pressure ranging from normal pressure to 200 kg/cm^2. The deprotection using an acid can be carried out with an acid such as hydrochloric acid, sulfuric acid, trifluoroacetic acid and trifluoromethanesulfonic acid in a solvent such as alcohols including methanol and ethanol, methylene chloride, 1,2-dichloroethane, 1,4-dioxane, tetrahydrofuran, toluene, and N,N-dimethylformamide in the presence or absence of a cation scavenger such as anisole and thioanisole at a temperature ranging from 0°C to the reflux temperature of a solvent.

[0049] In the eleventh synthetic method of the compounds of the present invention, the compound of the general formula (I) wherein R^3 is a saturated nitrogen-containing heterocyclic group which is substituted with oxo group can be obtained by reacting the compound of the general formula (I) wherein R^3 is a saturated nitrogen-containing heterocyclic group which is substituted with ethylenedioxy group, with an acid such as hydrochloric acid, an ethyl acetate solution of hydrogen chloride, an ethanolic solution of hydrogen chloride, sulfuric acid, hydrobromic acid, trifluoroacetic acid, p-toluenesulfonic acid, formic acid and acetic acid in the presence or absence of a solvent such as ethyl acetate, methylene chloride, 1,4-dioxane, tetrahydrofuran, methanol, ethanol, n-propanol and N,N-dimethylformamide, or a water-containing solvent thereof at a temperature ranging from 0°C to 200°C.

[0050] In the twelfth synthetic method of the compounds of the present invention, the compound of the general formula (I) wherein R^3 is a saturated nitrogen-containing heterocyclic group which is substituted with hydroxyimino group or an alkoxyimino group can be obtained by reacting the compound of the general formula (I) wherein R^3 is a saturated nitrogen-containing heterocyclic group which is substituted with oxo group, that is obtained by the eleventh synthetic method, with a compound represented by the following general formula (XVIII):

$$R^7\text{-O-NH}_2 \qquad \text{(XVIII)}$$

wherein R^7 represents hydrogen atom or an alkyl group,
in the presence or absence of a base such as triethylamine, diisopropylethylamine, sodium carbonate, potassium carbonate, sodium hydrogencarbonate and sodium acetate in a solvent such as alcohols including methanol, ethanol and n-propanol, N,N-dimethylformamide, 1,4-dioxane, tetrahydrofuran, and toluene at a temperature ranging from 0°C

to the reflux temperature of a solvent.

[0051] In the thirteenth synthetic method of the compounds of the present invention, the compound of the general formula (I) wherein R^2 is hydrogen atom can be obtained by subjecting the compound of the general formula (I) wherein R^2 is chlorine atom to catalytic reduction using a metal catalyst such as platinum and palladium/carbon in the presence or absence of an acid such as hydrochloric acid and acetic acid in an alcohol solvent such as methanol and ethanol or a water-containing solvent thereof under normal pressure at a temperature ranging from room temperature to the reflux temperature of a solvent.

[0052] In the fourteenth synthetic method of the compounds of the present invention, the compound of the general formula (I), wherein R^3 is a saturated nitrogen-containing heterocyclic group having an appropriate substituent on the nitrogen atom which is not bound to the adjacent $(CH_2)_m$ group, can be obtained by reacting an appropriate reagent with the compound of the general formula (I) wherein R^3 is a saturated nitrogen-containing heterocyclic group not having a protecting group on the nitrogen atom which is not bound to the adjacent $(CH_2)_m$ group

[0053] The reaction can be carried out in the presence or absence of a solvent such as N,N-dimethylformamide, methylene chloride, tetrahydrofuran, toluene, pyridine, nitrobenzene, 1,2-dichloroethane, 1,4-dioxane, methanol, ethanol, n-propanol and water, as well as a mixed solvent thereof, in the presence or absence of a base such as triethylamine and potassium carbonate at a temperature ranging from 0°C to 200°C.

[0054] Examples of the appropriate reagent include, for example, alkyl halides, triphenylmethyl chloride, benzyl chloride, benzhydryl chloride, a mixture of formic acid and formalin, acetyl chloride, acetic anhydride, trifluoroacetic anhydride, benzoyl chloride, benzyl chlorocarbonate, ethyl chlorocarbonate, di-tert-butyl dicarbonate, sodium cyanate, alkyl isocyanates, sodium thiocyanate, alkyl isothiocyanates, 1H-pyrazole-1-carboxamidine, methanesulfonyl chloride, p-toluenesulfonyl chloride, p-fluorobenzenesulfonyl chloride, urethanes, alkylurethanes, thiourethanes, alkylthiourethanes and the like.

[0055] In the fifteenth synthetic method of the compounds of the present invention, the compound of the general formula (I), wherein R^3 is a saturated nitrogen-containing heterocyclic group substituted with an alkoxycarbonyl group or benzyloxycarbonyl group on the nitrogen atom which is not bound to the adjacent $(CH_2)_m$ group, can be obtained by reacting the compound of the general formula (I) wherein R^3 is a saturated nitrogen-containing heterocyclic group substituted with an alkyl group or benzyl group on the nitrogen atom which is not bound to the adjacent $(CH_2)_m$ group with an alkyl chlorocarbonate or benzyl chlorocarbonate in the presence or absence of a solvent such as methylene chloride and toluene in the presence or absence of a base such as triethylamine and potassium carbonate at a temperature ranging from 0°C to 200°C.

[0056] Some of the compounds represented by the general formulas (III) to (VIII) which are starting materials or synthetic intermediates in the preparations of the compounds of the present invention are known compounds, which are disclosed in, for example, Journal of Medicinal Chemistry, Vol. 18, p. 726 (1975); Vol. 33, p. 1880 (1990); and Vol. 40, p. 1779 (1997); International Patent Publication No. 97/20820; European Patent Publication No. 223124 (1987) and the like, and can be prepared according to the method described therein. The preparations of some novel compounds will be described in reference examples.

[0057] The medicaments which comprise as an active ingredient the novel 1H-imidazopyridine derivative represented by the aforementioned general formula (I) or (II) or a salt thereof are generally administered as oral preparations in the forms of capsules, tablets, fine granules, granules, powders, syrups, dry syrups and the like, or as parenteral preparations in the forms of injections, suppositories, eye drops, eye ointments, ear drops, nasal drops, dermal preparations, inhalations and the like. These formulations can be manufactured according to conventional methods by addition of pharmacologically and pharmaceutically acceptable additives. For example, in the oral preparations and suppositories, pharmaceutical ingredients may be used such as excipients such as lactose, D-mannitol, corn starch, and crystalline cellulose; disintegrators such as carboxymethylcellulose and carboxymethylcellulose calcium; binders such as hydroxypropylcellulose, hydroxypropylmethylcellulose, and polyvinylpyrrolidone; lubricants such as magnesium stearate and talc; coating agents such as hydroxypropylmethylcellulose, sucrose, and titanium oxide; bases such as polyethylene glycol and hard fat and the like. In injections, or eye or ear drops and the like, pharmaceutical ingredients may be used such as solubilizers or solubilizing aids which may constitute aqueous preparations or those dissolved upon use such as distilled water for injection, physiological saline, and propylene glycol; pH modifiers such as inorganic or organic acids or bases; isotonicities such as sodium chloride, glucose, and glycerin; stabilizers and the like; and in eye ointments and dermal preparations, pharmaceutical ingredients which are suitable for ointments, creams and patches such as white vaseline, macrogols, glycerin, and cotton cloth.

[0058] A dose of the compounds of the present invention to a patient under therapeutic treatment is generally from about 0.1 to 1,000 mg in oral administration, and from about 0.01 to 500 mg in parenteral administration for an adult, which may depend on the symptoms of the patient. The aforementioned dose can be administered once a day or several times a day as divided portions. However, it is desirable that the aforementioned dose may suitably be increased or decreased according to a purpose of a therapeutic or preventive treatment, part or type of a disease, and the age or symptoms of a patient.

Examples

[0059] The present invention will be explained by referring to Reference Examples and Working Examples However, the scope of the present invention is not limited to these examples.

[0060] The abbreviations in the tables have the following meanings: Ph, phenyl; Bn, benzyl; Boc, tert-butoxycarbonyl; Ac, acetyl; Ms, methanesulfonyl; Ts, p-toluenesulfonyl; Me, methyl; Et, ethyl; n-Bu, n-butyl.

Reference example 1

Ethyl N-triphenylmethyl-4-piperidinecarboxylate

[0061] To a solution of 76 5 g of ethyl isonipecotate and 81.5 ml of triethylamine in 750 ml of methylene chloride, 149 g of triphenylmethyl chloride divided in three portions was added portionwise at room temperature, and the mixture was stirred for 16 hours. The reaction mixture was added with water and extracted with methylene chloride. The extract was washed successively with water and saturated brine, and dried, and then the solvent was evaporated. The resulting brown liquid was added with diisopropyl ether, and the precipitated crystals were collected by filtration and washed with diisopropyl ether to give 184 g of pale yellow crystals. Recrystallization from ethanol gave colorless prisms having the melting point of from 147.5 to 148.5°C.

Elemental analysis for $C_{27}H_{29}NO_2$			
Calculated %	C, 81.17;	H, 7.32;	N, 3.51
Found %	C, 81.19;	H, 7.22;	N, 3.44

Reference example 2

N-Triphenylmethyl-4-piperidinemethanol

[0062] To a suspension of 10.6 g of lithium aluminium hydride in 300 ml of dried tetrahydrofuran, a solution of 112 g of ethyl N-triphenylmethyl-4-piperidine-carboxylate in 400 ml of dried tetrahydrofuran was added dropwise under ice-cooling, and the mixture was stirred at room temperature for 4 hours. The reaction mixture was added dropwise with a mixture of tetrahydrofuran and 10% aqueous sodium hydroxide solution under ice-cooling. An insoluble matter was filtered off and washed with tetrahydrofuran. The filtrates were combined and concentrated to give a colorless solid. The colorless solid was washed with methanol to give 84.2 g of colorless crystals. Recrystallization from methanol gave colorless crystals having the melting point of from 92 to 99.5°C.

Elemental analysis for $C_{25}H_{27}NO$			
Calculated %	C, 83.99;	H, 7.61;	N, 3.92
Found %	C, 83.79;	H, 7.74;	N, 3.94

[0063] In accordance with the method of Reference example 2, the compound of Reference example 3 was obtained.

Reference example 3

N-Triphenylmethyl-4-piperidineethanol

[0064]

Appearance: colorless liquid
NMR spectrum δ ($CDCl_3$)ppm: 1.26(1H,brs), 1.36(2H,brs), 1.45-1.58(4H,m), 1.67(2H,d, J=12Hz), 3.05(2H,brs), 3.74(2H,t,J=6Hz), 7.14(3H,t,J=7.5Hz), 7.24(6H,t,J=7.5Hz), 7.46(6H,brs)
IR spectrum ν (liq.)cm^{-1}: 3416
Mass spectrum m/z: 371(M^+)

Reference example 4

(N-Triphenylmethyl-4-piperidyl)methyl methanesulfonate

[0065] To a solution of 84.0 g of N-triphenylmethyl-4-piperidinemethanol and 36.2 ml of triethylamine in 420 ml of dried tetrahydrofuran, 18 3 ml of methanesulfonyl chloride was added dropwise under ice-cooling, and the mixture was stirred at room temperature for 5 5 hours. The reaction mixture was added with water and extracted with diethyl ether The extract was washed successively with water and saturated brine, and dried, and then the solvent was evaporated. The resulting residue was added with a mixture of isopropanol and methanol, and the precipitated crystals were collected by filtration and washed with methanol to give 90 4 g of colorless crystals. Recrystallization from a mixture of methylene chloride and methanol gave colorless prisms having the melting point of from 129.5 to 134°C.

Elemental analysis for $C_{26}H_{29}NO_3S$			
Calculated %	C, 71 69;	H, 6.71;	N, 3.22
Found %	C, 71 68;	H, 6.47;	N, 3.19

[0066] In accordance with the method of Reference example 4, the compound of Reference example 5 was obtained.

Reference example 5

2-(N-Triphenylmethyl-4-piperidyl)ethyl methanesulfonate

[0067]

Appearance: colorless crystals
Recrystallization solvent: methanol - diethyl ether
mp: 111.5-114°C

Elemental analysis for $C_{27}H_{31}NO_3S$			
Calculated %	C, 72.13;	H, 6.95;	N, 3.12
Found %	C, 72.03;	H, 7.12;	N, 3.14

Reference example 6

4-Azidomethyl-N-triphenylmethylpiperidine

[0068] A suspension of 60 0 g of (N-triphenylmethyl-4-piperidyl)methyl methanesulfonate and 17.9 g of sodium azide in 300 ml of dried N,N-dimethyl-formamide was stirred at 70°C for 17 hours. After the reaction, an insoluble matter was filtered off and the filtrate was concentrated. The resulting residue was added with water and extracted with ethyl acetate. The extract was washed successively with water and saturated brine, and dried, and then the solvent was evaporated. The resulting solid was washed successively with ethanol and n-hexane to give 42.6 g of colorless crystals. Recrystallization from a mixture of methanol and diethyl ether gave colorless crystals having the melting point of from 103.5 to 105.5°C.

Elemental analysis for $C_{25}H_{26}N_4$			
Calculated %	C, 78.50;	H, 6.85;	N, 14.65
Found %	C, 78.45;	H, 6.74;	N, 14.82

Reference example 7

tert-Butyl 2-(2-azidoethyl)-1-piperidinecarboxylate

[0069] To a solution of 46.7 g of tert-butyl 2-(2-hydroxyethyl)-1-piperidine-carboxylate and 31.3 ml of triethylamine in 300 ml of dried tetrahydrofuran, 15.8 ml of methanesulfonyl chloride was added dropwise under ice-cooling, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was added with water and extracted with diethyl ether. The extract was washed successively with water and saturated brine, and dried, and then the solvent was evaporated. The resulting solid was washed with n-heptane to give 54.4 g of colorless crystals. And then, 22.9 g of sodium azide and 220 ml of N,N-dimethylformamide were added to the resulting crystals, and the mixture was stirred at 70°C for 4 hours. After the reaction, an insoluble matter was filtered off and the filtrate was concentrated. The resulting residue was added with water and extracted with ethyl acetate. The extract was washed successively with water and saturated brine, and dried, and then the solvent was evaporated to give 43 2 g of a yellow liquid

NMR spectrum δ (DMSO-d_6)ppm: 1.20-1.32(1H,m),1.40(9H,s),1.48-1.58(5H,m),1.60-1 .68(1H,m),1.88-1.96(1H, m),2 71-2 78(1H,m),3.28(2H,t,J=6.5Hz),3 80-3.86(1H,m),4,19-4.25(1H,m)
IR spectrum ν (liq)cm^{-1}: 2104,1692

Reference example 8

4-Oxo-1-piperidineacetonitrile

[0070] A suspension of 25.0 g of 4-piperidinone monohydrochloride monohydrate, 11.5 ml of chloroacetonitrile and 57 0 ml of diisopropylethylamine in 250 ml of tetrahydrofuran was refluxed for 10 hours. After the reaction, an insoluble matter was filtered off. The filtrate was added with saturated aqueous sodium hydrogencarbonate solution and extracted with a mixture of ethyl acetate and methanol (10:1). The extract was dried, and the solvent was evaporated to give brown crystals. The crystals were washed with a mixture of ethyl acetate and n-heptane to give 15.7 g of pale brown crystals

NMR spectrum δ ($CDCl_3$)ppm: 2.53(4H,t,J=6Hz),2 91(4H,t,J=6Hz),3 66(2H,s)
IR spectrum ν (KBr)cm^{-1}: 2232,1714
Mass spectrum m/z: 138(M^+)

[0071] In accordance with the method of Reference example 8, the compound of Reference example 9 was obtained.

Reference example 9

4-(tert-Butoxycarbonylamino)-1-piperidineacetonitrile

[0072]

Appearance: colorless needles
Recrystallization solvent: methanol
mp: 147-148°C

Elemental analysis for $C_{12}H_{21}N_3O_2$			
Calculated %	C, 60.23;	H, 8.84;	N, 17.56
Found %	C, 60.08;	H, 8.63;	N, 17.55

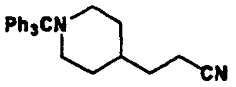
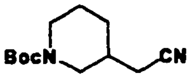
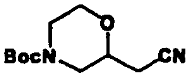
Reference example 10

N-Triphenylmethyl-4-piperidineacetonitrile

[0073] A suspension of 90.4 g of (N-triphenylmethyl-4-piperidyl)methyl methanesulfonate, 3.50 g of potassium iodide and 20.3 g of sodium cyanide in 400 ml of dried dimethylsulfoxide was stirred at 90°C for 5 hours. The reaction mixture was added with water and extracted with ethyl acetate. The extract was washed successively with water and saturated brine, and dried, and the solvent was evaporated to give a yellow liquid. The liquid was added with methanol, and the precipitated crystals were collected by filtration and washed with methanol to give 70.0 g of colorless crystals. Recrystallization from a mixture of methylene chloride and methanol gave colorless crystals having the melting point of from 138 to 139°C.

Elemental analysis for $C_{26}H_{26}N_2$			
Calculated %	C, 85 21;	H, 7.15;	N, 7.64
Found %	C, 85 35;	H, 7.26;	N, 7.62

[0074] In accordance with the method of Reference example 10, the compounds of Reference examples 11 through 13 were obtained

Reference example		Physical properties (Recrystallization solvent)
11		colorless crystals (MeOH-Et_2O) mp,158.5-160.5°C Elemental analysis for $C_{27}H_{28}N_2$ Calcd. %: C, 85.22; H, 7.42; N, 7.36 Found %: C, 85.21; H, 7.52; N, 7.34
12		colorless prisms (iso-Pr_2O-n-Heptane) mp,48-49°C Elemental analysis for $C_{12}H_{20}N_2O_2$ Calcd. %: C, 64.26; H, 8.99; N, 12.49 Found %: C, 64.01; H, 9.24; N, 12.35
13		colorless crystals (iso-Pr_2O) mp,89-90°C Elemental analysis for $C_{11}H_{18}N_2O_3$ Calcd. %: C, 58.39; H, 8.02; N, 12.38 Found %: C, 58.31; H, 8.01; N, 12.37

Reference example 14

N-Triphenylmethyl-4-piperidineacetic acid

[0075] A suspension of 21.2 g of N-triphenylmethyl-4-piperidineacetonitrile, 127 ml of 10% aqueous sodium hydroxide solution and 312 ml of ethanol was refluxed for 74 hours. The reaction mixture was neutralized with 10 % hydrochloric acid under ice-cooling, and then adjusted to pH 4-5 with 10% aqueous citric acid solution. The precipitated crystals were collected by filtration, and washed successively with water and methanol to give 23.6 g of colorless crystals. Recrystallization from a mixture of methanol and ethyl acetate gave colorless needles having the melting point of from 197 to 209°C (decomposition).

Elemental analysis for $C_{26}H_{27}NO_2$			
Calculated %	C, 81.01;	H, 7.06;	N, 3.63
Found %	C, 80.85;	H, 7.17;	N, 3.70

Reference example 15

Ethyl N-triphenylmethyl-4-piperidineacetate

[0076] A suspension of 23.6 g of N-triphenylmethyl-4-piperidineacetic acid, 16.9 g of potassium carbonate and 5.0 ml of ethyl bromide in 230 ml of dried N,N-dimethylformamide was stirred at 90°C for 5 hours. After cooling, the reaction mixture was added with water and ethyl acetate, and the precipitated crystals were collected by filtration and washed with water to give 20.6 g of colorless crystals. Recrystallization from a mixture of methanol and tetrahydrofuran gave colorless crystals having the melting point of from 165 to 166°C

Elemental analysis for $C_{28}H_{31}NO_2$			
Calculated %	C, 81.32;	H, 7.56;	N, 3.39
Found %	C, 81.08;	H, 7.69;	N, 3.43

Reference example 16

4,4-Ethylenedioxy-1-piperidineacetonitrile

[0077] A solution of 10.0 g of 4-oxo-1-piperidineacetonitrile, 22.6 g of ethylene glycol and 0.62 g of anhydrous p-toluenesulfonic acid in 100 ml of toluene was refluxed for 6 hours with Dean-stark dehydrating apparatus After cooling, the reaction mixture was added with saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was dried, and the solvent was evaporated to give a pale brown liquid. The resulting liquid was purified by alumina column chromatography using ethyl acetate - n-heptane (1:3) as an eluting solvent to give 12.8 g of a colorless liquid.

NMR spectrum δ ($CDCl_3$)ppm : 1.78(4H,t,J=6Hz),2.69(4H,t,J=6Hz),3.52(2H,s),3.96(4 H,s)
IR spectrum ν (liq.)cm^{-1}: 2230,1094
Mass spectrum m/z: 182(M^+)

Reference example 17

4-Aminomethyl-N-triphenylmethylpiperidine

[0078] To a suspension of 4.70 g of lithium aluminium hydride in 250 ml of dried tetrahydrofuran, a solution of 47.7 g of 4-azidomethyl-N-triphenylmethylpiperidine in 250 ml of dried tetrahydrofuran was added dropwise under ice-cooling, and the mixture was stirred at room temperature for 4 hours. The reaction mixture was added dropwise with a mixture of tetrahydrofuran and 10% aqueous sodium hydroxide solution under ice-cooling. An insoluble matter in the mixture was filtered off, and washed with tetrahydrofuran. The filtrate and the washings were combined and concentrated to give 48.1 g of a colorless liquid.

NMR spectrum δ ($CDCl_3$)ppm: 1.14(1H,brs),1.36(2H,brs),1.48(2H,qd,J=5,2.5Hz),1.68 (2H,d,J=11.5Hz),2.59(2H, d,J=6Hz),3 10(2H,brs),7 14(3H,t,J=7.5Hz),7.25(6H,t,J=7.5Hz),7.47(6H,brs)
IR spectrum ν (liq.)cm^{-1}: 3056,3028
High resolution mass spectrum: Analysis for $C_{25}H_{28}N_2$

Calculated m/z: 356.2252
Found m/z: 356.2250

Reference example 18

4-(2-Aminoethyl)-N-triphenylmethylpiperidine

[0079] To a suspension of 21.7 g of lithium aluminium hydride in 300 ml of dried tetrahydrofuran, a solution of 28.1 g of concentrated sulfuric acid in 100 ml of dried tetrahydrofuran was added dropwise under ice-cooling, and the mixture was stirred for 30 minutes. And then, a solution of 70.0 g of N-triphenylmethyl-4-piperidineacetonitrile in 300 ml of dried tetrahydrofuran was added dropwise to the mixture under ice-cooling, and the mixture was stirred at room temperature for 6 hours. The reaction mixture was added dropwise with a mixture of tetrahydrofuran and 10% aqueous sodium hydroxide solution under ice-cooling. An insoluble matter in the mixture was filtered off, and the filtrate was concentrated The resulting residue was added with water and extracted with ethyl acetate The extract was washed with saturated brine, and dried, and the solvent was evaporated to give 71 4 g of a colorless liquid

NMR spectrum δ ($CDCl_3$)ppm: 1.18(1H,brs),1.35(2H,brs),1.40(2H,q,J=7.5Hz),1.48(2 H,qd,J=11.5,3Hz),1.63(2H, d,J=11.5Hz),2 67(2H,t,J=7 5Hz),3.05(2H,brs),7.14(3H,t,J=7. 5Hz),7.24(6H,t,J=7 5Hz),7.47(6H,brs)
IR spectrum ν (liq)cm^{-1}: 3060,3032
High resolution mass spectrum: Analysis for $C_{26}H_{30}N_2$

Calculated m/z: 370.2409
Found m/z: 370.2400

[0080] In accordance with the method of Reference example 18, the compound of Reference example 19 was obtained.

Reference example 19

4-(3-Aminopropyl)-N-triphenylmethylpiperidine

[0081]

Appearance: colorless liquid
NMR spectrum δ (DMSO-d_6)ppm: 0.95-1.05(1H,m),1.19-1.35(6H,m),1.41(2H,q,J=11.5Hz),1.62(2H,d,J=11.5Hz), 2.47(2H,t,J=6.5Hz),2.93(2H,d,J=11.5 Hz),7.15(3H,t,J=7.5Hz),7.28(6H,t,J=7.5Hz),7.38(6H,d,J=7.5Hz)
IR spectrum ν (liq.)cm^{-1}: 2972,2920

Reference example 20

tert-Butyl 2-(2-aminoethyl)-1-piperidinecarboxylate

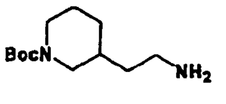
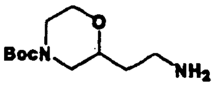
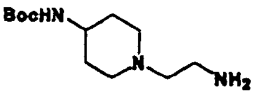
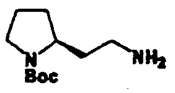
[0082] A suspension of 43.0 g of tert-butyl 2-(2-azidoethyl)-1-piperidinecarboxylate and 2.15 g of 5% palladium on carbon in 215 ml of methanol was catalytically hydrogenated at room temperature for 9 hours. After the reaction, the catalyst was filtered off, and the filtrate was concentrated to give 37.2 g of a colorless liquid. NMR spectrum δ (DMSO-d_6)ppm: 1.20-1.30(1H,m),1.38(9H,s),1.45-1.58(4H,m),1.72-1 .82(1H,m),2.34-2.47(2H,m),2.65-2.76(1H,m),3.18(2H,t, J=6Hz),3.78-3.85(1H,m),4 13-4. 20(1H,m)
IR spectrum ν (liq.)cm^{-1}: 2976,2936,1692

Reference example 21

1-(2-Aminoethyl)-4,4-ethylenedioxypiperidine

[0083] A suspension of 12.7 g of 4,4-ethylenedioxy-1-piperidineacetonitrile, 1.3 ml of Raney nickel and 113 ml of 2% methanolic solution of ammonia was catalytically hydrogenated at room temperature under 50 atm for 20 hours. After the reaction, the catalyst was filtered off, and the filtrate was concentrated. The resulting pale green liquid was purified by alumina column chromatography [eluting solvent: ethyl acetate →ethyl acetate - methanol (10:1)] to give 10.1 g of a colorless liquid.
NMR spectrum δ (DMSO-d_6)ppm : 1.58(4H,t,J=6Hz),2.37(2H,t,J=6.5Hz),2.42(4H,t,J= 6Hz),2.57(2H,t,J=6.5Hz),3.84 (4H,s)
IR spectrum ν (liq.)cm^{-1}: 2956,2884,1094

[0084] In accordance with the method of Reference example 21, the compounds of Reference examples 22 through 25 were obtained.

Reference example		Physical properties
22		colorless liquid NMR spectrum δ (DMSO-d_6)ppm:1.02-1.12(1H,m),1.16-1.50(14H,m),1.53-1.60(1H,m),1.70-1.77(1H,m),2.56(2H,t,J=7.5Hz),2.75-2.83(1H,m),3.65-3.78(2H,m) IR spectrum ν (liq.) cm^{-1}:2980,2936,1692
23		bluish green liquid NMR spectrum δ (DMSO-d_6)ppm:1.40(9H,s),1.55-2.00(2H,m),2.50-2.65(1H,m),2.75-2.90(1H,m),2.90-3.50(4H,m),3.60-3.90(3H,m) IR spectrum ν (liq.) cm^{-1}:1700
24		dark green liquid NMR spectrum δ ($CDCl_3$)ppm:1.15(2H,brs),1.45(9H,s),1.85-2.00(2H,m),2.00-2.20(2H,m),2.30-2.50(2H,m),2.60-2.95(4H,m),3.40-3.60(2H,m),4.46(1H,brs) IR spectrum ν (liq.) cm^{-1}:3332,1692
25		colorless liquid NMR spectrum δ (DMSO-d_6)ppm:1.39(9H,s),1.58-1.66(1H,m),1.68-1.90(5H,m),2.47(2H,t,J=7.5Hz),3.13-3.22(2H,m),3.68-3.76(1H,m) IR spectrum ν (liq.) cm^{-1}:2972,2876,1696 Specific rotation $[\alpha]_D^{20}$: -54.3° (c=0.1, DMSO)

Reference example 26

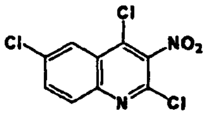
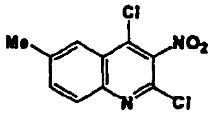
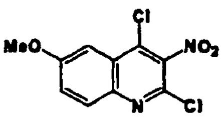
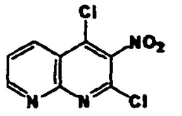
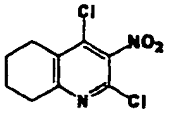
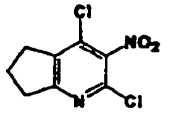
5,7-Dichloro-6-nitrothieno[3,2-b]pyridine

[0085] A mixture of 24.8 g of 4,5-dihydro-7-hydroxy-6-nitrothieno[3,2-b]pyridine-5-one and 87 ml of phosphorus oxychloride was stirred at 60°C for 24 hours. The reaction solution was concentrated and the residue was dissolved in a mixture of methylene chloride and methanol (10:1), and then the solution was poured into water. An insoluble matter was filtered off, and the organic solvent layer was separated. Furthermore, the aqueous layer was extracted with a mixture of methylene chloride and methanol (10:1). The combined organic solvent layer was dried, and the solvent was evaporated to give brown crystals. The resulting brown crystals were purified by silica gel column chromatography using ethyl acetate - n-hexane (1:3) as an eluting solvent to give 10.6 g of pale brown crystals. Recrystallization from n-hexane gave pale brown crystals having the melting point of from 96 to 97°C.

NMR spectrum δ ($CDCl_3$)ppm: 7.61(1H,d,J=5 5Hz),8.07(1H,d,J=5.5Hz)
IR spectrum ν (KBr)cm^{-1}: 1540,1368
Mass spectrum m/z : 248,250,252(M+,9:6:1)

[0086] In accordance with the method of Reference example 26, the compounds of Reference examples 27 through

32 were obtained.

Reference example		Physical properties (Recrystallization solvent)
27		pale brown crystals NMR spectrum δ ($CDCl_3$)ppm:7.87(1H,dd,J=9,2.5Hz),8.06(1H,d,J=9Hz),8.24(1H,d,J=2.5Hz)
28		brown crystals NMR spectrum δ (DMSO-d_6)ppm:2.62(3H,s),7.78(1H,dd,J=9,2Hz),7.96(1H,d,J=2Hz),8.05(1H,d,J=9Hz)
29		pale brown crystals NMR spectrum δ ($CDCl_3$)ppm:4.01(3H,s),7.42(1H,d,J=2.5Hz),7.55(1H,dd,J=9,2.5Hz),7.99(1H,d,J=9 Hz)
30		yellow crystals (iso-PrOH) mp,182-183°C Elemental analysis for $C_8H_3Cl_2N_3O_2$ Calcd. %: C, 39.37; H, 1.24; N, 17.22 Found %: C, 39.37; H, 1.02; N, 17.25
31		pale brown plates (n-Hexane) mp,64-64.5°C Elemental analysis for $C_9H_8Cl_2N_2O_2$ Calcd. %: C, 43.75; H, 3.26; N, 11.34 Found %: C, 43.77; H, 3.02; N, 11.44
32		pale yellow plates (n-Hexane) mp,94.5-95.5°C Elemental analysis for $C_8H_6Cl_2N_2O_2$ Calcd. %: C, 41.23; H, 2.59; N, 12.02 Found %: C, 41.12; H, 2.64; N, 12.01

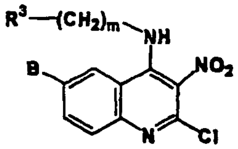
Reference example 33

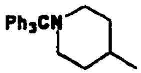
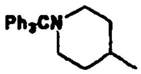
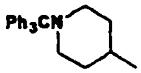
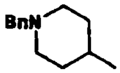
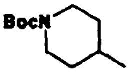
2-Chloro-3-nitro-4-[2-(N-triphenylmethyl-4-piperidyl)ethylamino]quinoline

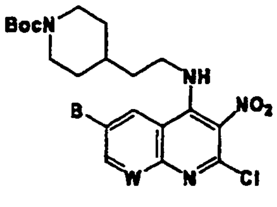
[0087] To a solution of 22 6 g of 2,4-dichloro-3-nitroquinoline and 13.0 ml of triethylamine in 60 ml of N,N-dimethylformamide, a solution of 23.0 g of 4-(2-aminoethyl)-N-triphenylmethylpiperidine in 40 ml of N,N-dimethylformamide was added dropwise with stirring under ice-cooling. The mixture was stirred at room temperature for 1 hour. The reaction mixture was added with ethyl acetate and water. The precipitated crystals were collected by filtration, and washed successively with ethyl acetate and diethyl ether to give 26.9 g of yellow crystals. Recrystallization from a mixture of N,N-dimethylformamide and ethyl acetate gave yellow crystals having the melting point of from 223.5 to 231°C (decomposition).

Elemental analysis for $C_{35}H_{33}ClN_4O_2$			
Calculated %	C, 72.84;	H, 5.76;	N, 9.71
Found %	C, 72.64;	H, 5.80;	N, 9.82

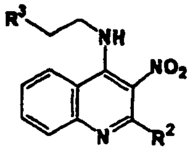
[0088] In accordance with the method of Reference example 33, the compounds of Reference examples 34 through 60 were obtained.

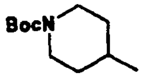
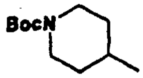
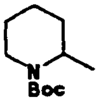
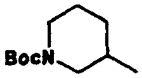
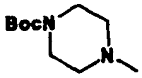


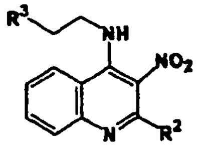
Reference example	B	R³	m	Physical properties (Recrystallization solvent)
34	Cl		2	yellow crystals(CH_2Cl_2-iso-Pr_2O) mp,196.5-199.5℃(decomposition) Elemental analysis for $C_{35}H_{32}Cl_2N_4O_2$ Calcd.%: C, 68.74; H, 5.27; N, 9.16 Found %:C, 68.47: H, 5.31: N, 9.18
35	H		1	yellow crystals(MeOH-THF) mp,214.5-225℃(decomposition) Elemental analysis for $C_{34}H_{31}ClN_4O_2$ Calcd.%: C, 72.52; H, 5.55; N, 9.95 Found %:C, 72.54; H, 5.62; N, 9.82
36	H		3	yellow crystals(MeOH-iso-Pr_2O) mp,176.5-183℃(decomposition) Elemental analysis for $C_{36}H_{35}ClN_4O_2$ Calcd.%: C, 73.14; H, 5.97; N, 9.48 Found %: C, 73.33; H, 6.04; N, 9.36
37	H		2	yellow crystals(MeOH) mp,128.5-129.5℃ Elemental analysis for $C_{23}H_{25}ClN_4O_2$ Calcd.%: C, 65.01; H, 5.93; N, 13.19 Found %: C, 64.96; H, 6.03; N, 13.27
38	H		0	yellow crystals(AcOEt) mp,199-202℃(decomposition) Elemental analysis for $C_{19}H_{23}ClN_4O_4$ Calcd.%: C, 56.09; H, 5.70; N, 13.77 Found%: C, 56.04; H, 5.69; N, 13.77

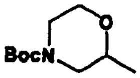
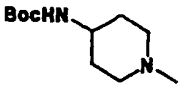
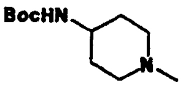
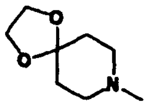


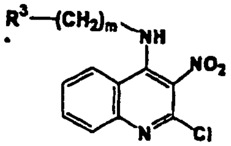
Reference example	B	W	Physical properties (Recrystallization solvent)
39	Cl	CH	yellow crystals(MeOH) mp,189.5-190.5℃ Elemental analysis for $C_{21}H_{26}Cl_2N_4O_4$ Calcd.%: C, 53.74; H, 5.58; N, 11.94 Found%: C, 53.61; H, 5.55; N, 11.67
40	Me	CH	yellowish orange crystals (MeOH) mp,185-186℃ Elemental analysis for $C_{22}H_{29}ClN_4O_4$ Calcd.%: C, 58.86; H, 6.51; N, 12.48 Found%: C, 58.72; H, 6.60; N, 12.39
41	MeO	CH	yellowish orange crystals (MeOH) mp,183.5-184.5℃ Elemental analysis for $C_{22}H_{29}ClN_4O_5$ Calcd.%: C, 56.83; H, 6.29; N, 12.05 Found%: C, 56.90; H, 6.34; N, 12.05
42	H	N	yellow crystals(AcOEt-Et_2O) mp,157.5-161℃ Elemental analysis for $C_{20}H_{26}ClN_5O_4$ Calcd.%: C, 55.11; H, 6.01; N, 16.07 Found%: C, 55.18; H, 6.10; N, 15.86

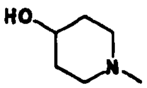
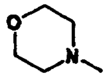
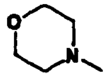
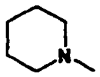
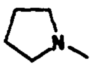


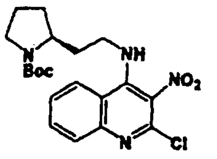
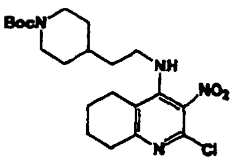
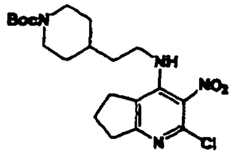
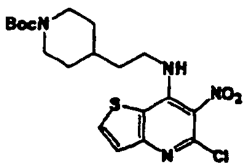
Reference example	R^2	R^3	Physical properties (Recrystallization solvent)
43	Cl		yellow crystals(AcOEt-iso-Pr_2O) mp,133-134℃ Elemental analysis for $C_{21}H_{27}ClN_4O_4$ Calcd.%: C, 57.99; H, 6.26; N, 12.88 Found%: C, 57.99; H, 6.34; N, 12.85
44	Me		yellow crystals(EtOH) mp,138-138.5℃ Elemental analysis for $C_{22}H_{30}N_4O_4$ Calcd.%: C, 63.75; H, 7.30; N, 13.52 Found%: C, 63.70; H, 7.49; N, 13.44
45	Cl		yellow needles (AcOEt-n-Heptane) mp,148.5-149℃ Elemental analysis for $C_{21}H_{27}ClN_4O_4$ Calcd.%: C, 57.99; H, 6.26; N, 12.88 Found%: C, 58.04; H, 6.27; N, 12.87
46	Cl		yellow crystals(iso-Pr_2O) mp,121-122.5℃ Elemental analysis for $C_{21}H_{27}ClN_4O_4$ Calcd.%: C, 57.99; H, 6.26; N, 12.88 Found%: C, 58.04; H, 6.32; N, 12.82
47	Cl		yellow prisms (MeOH-iso-Pr_2O) mp,155-157℃ Elemental analysis for $C_{20}H_{26}ClN_5O_4$ Calcd.%: C, 55.11; H, 6.01; N, 16.07 Found%: C, 54.92; H, 5.89; N, 16.00



Reference example	R²	R³	Physical properties (Recrystallization solvent)
48	Cl		yellow crystals (MeOH) mp,176.5–177.5℃ Elemental analysis for $C_{20}H_{25}ClN_4O_5$ Calcd.%: C, 54.98; H, 5.77; N, 12.82 Found%: C, 54.85; H, 5.76; N, 12.86
49	Cl		yellow needles (AcOEt–iso–Pr_2O) mp,150–150.5℃ Elemental analysis for $C_{21}H_{28}ClN_5O_4$ Calcd.%: C, 56.06; H, 6.27; N, 15.57 Found%: C, 55.92; H, 6.19; N, 15.59
50	Me		yellow crystals (AcOEt) mp,151–151.5℃ Elemental analysis for $C_{22}H_{31}N_5O_4$ Calcd.%: C, 61.52; H, 7.27; N, 16.31 Found%: C, 61.33; H, 7.14; N, 16.29
51	Cl		yellow fine needles (AcOEt–iso–Pr_2O) mp,119.5–123℃ Elemental analysis for $C_{18}H_{21}ClN_4O_4 \cdot 1/4H_2O$ Calcd.%: C, 54.41; H, 5.45; N, 14.10 Found%: C, 54.60; H, 5.45; N, 14.19



Reference example	R^3	m	Physical properties (Recrystallization solvent)
52		2	yellow prisms (AcOEt-n-Heptane) mp,121-123℃ Elemental analysis for $C_{16}H_{19}ClN_4O_3$ Calcd.%: C, 54.78; H, 5.48; N, 15.97 Found%: C, 54.70; H, 5.51; N, 15.93
53		2	yellow crystals (MeOH) mp,123-124℃ Elemental analysis for $C_{15}H_{17}ClN_4O_3$ Calcd.%: C, 53.50; H, 5.09; N, 16.64 Found%: C, 53.44; H, 4.94; N, 16.60
54		3	yellowish brown crystals (MeOH) mp,163-164℃ Elemental analysis for $C_{16}H_{19}ClN_4O_3$ Calcd.%: C, 54.78; H, 5.48; N, 15.97 Found%: C, 54.79; H, 5.36; N, 15.95
55		2	yellowish brown crystals (MeOH) mp,145-146℃ Elemental analysis for $C_{16}H_{19}ClN_4O_2$ Calcd.%: C, 57.40; H, 5.72; N, 16.73 Found%: C, 57.23; H, 5.75; N, 16.74
56		2	yellow crystals (iso-Pr_2O) mp,102.5-103℃ Elemental analysis for $C_{15}H_{17}ClN_4O_2$ Calcd.%: C, 56.16; H, 5.34; N, 17.47 Found%: C, 56.14; H, 5.37; N, 17.41

Reference example		Physical properties (Recrystallization solvent)
57		yellow prisms (iso-Pr_2O-n-Heptane) mp,96–98℃ Elemental analysis for $C_{20}H_{23}ClN_4O_4$ Calcd.%: C, 57.07; H, 5.99; N, 13.31 Found%: C, 57.04; H, 5.92; N, 13.26 Specific rotation $[\alpha]_D^{20}$: -97.3° (c=0.1, DMSO)
58		pale yellow crystals (MeOH) mp,135–135.5℃ Elemental analysis for $C_{21}H_{31}ClN_4O_4$ Calcd.%: C, 57.46; H, 7.12; N, 12.76 Found%: C, 57.33; H, 7.15; N, 12.74
59		red liquid NMR spectrum δ ($DMSO-d_6$)ppm:0.98(2H,q,J=12.5Hz),1.20–1.30(1H,m),1.41(9H,s),1.59(2H,d,J=12.5Hz),2.04(2H,quin,J=8Hz),2.60–2.72(4H,m),2.79(2H,t,J=8Hz),2.93(2H,t,J=8Hz),3.21(2H,q,J=6.5Hz),3.89(2H,d,J=12.5Hz),6.52(1H,t,J=6.5Hz) IR spectrum ν (liq.) cm^{-1}:1688,1526,1366
60		orange crystals (iso-PrOH) mp,148.5–150℃ Elemental analysis for $C_{19}H_{25}ClN_4O_4S$ Calcd.%: C, 51.75; H, 5.71; N, 12.71 Found%: C, 51.64; H, 5.80; N, 12.69

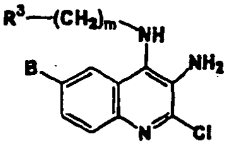
Reference example 61

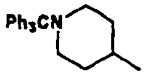
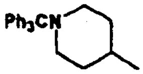
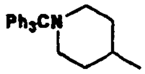
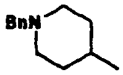
3-Amino-2-chloro-4-[2-(N-triphenylmethyl-4-piperidyl)ethylamino]quinoline

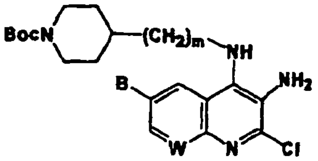
[0089] To a solution of 6.56g of nickel chloride hexahydrate and 22 3 ml of methanol in 100 ml of tetrahydrofuran, 2.09 g of sodium borohydride was added portionwise under ice-cooling, and then a suspension of 31.9 g of 2-chloro-3-nitro-4-[2-(N-triphenylmethyl-4-piperidyl)ethylamino]quinoline in 300 ml of tetrahydrofuran was added to the mixture. Successively, 8 35 g of sodium borohydride divided in four portions was added portionwise, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was added with 50 ml of water and an insoluble matter was filtered off, and then the extract was concentrated. The residue was added with water and extracted with ethyl acetate. The extract was washed successively with water and saturated brine, and dried, and then the solvent was evaporated. The resulting pale green liquid was solidified with a mixture of ethyl acetate and diisopropyl ether, and the solid was washed successively with isopropanol and diisopropyl ether to give 20.1 g of pale green crystals. Recrystallization from isopropanol gave pale green crystals having the melting point of from 116 to 121°C.

Elemental analysis for $C_{35}H_{35}ClN_4$			
Calculated %	C, 76.83;	H, 6.45;	N, 10 24
Found %	C, 76.74;	H, 6.54;	N, 10 17

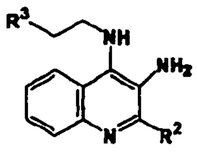
[0090] In accordance with the method of Reference example 61, the compounds of Reference examples 62 through 88 were obtained.

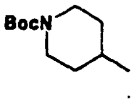
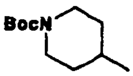
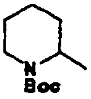
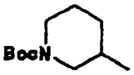
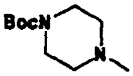


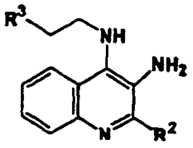
Reference example	B	R^3	m	Physical properties (Recrystallization solvent)
62	Cl		2	colorless crystals (EtOH) mp,197-198.5℃ Elemental analysis for $C_{35}H_{34}Cl_2N_4$ Calcd.%: C, 72.28; H, 5.89; N, 9.63 Found%: C, 72.45; H, 6.17; N, 9.34
63	H		1	brown liquid NMR spectrum δ (DMSO-d_6)ppm:1.20-1.45(3H,m),1.49(2H,q,J=11.5Hz),1.72(2H,d,J=11.5Hz),3.18(2H,t,J=7Hz),4.89(2H,s),5.09(1H,t,J=7Hz),7.14(3H,t,J=7.5Hz),7.27(6H,t,J=7.5Hz),7.35-7.45(8H,m),7.68(1H,d,J=8Hz),7.99(1H,d,J=8Hz) IR spectrum ν (liq.) cm^{-1}:3356,3056
64	H		3	colorless crystals (iso-Pr_2O) mp,149-158℃ Elemental analysis for $C_{36}H_{37}ClN_4$ Calcd.%: C, 77.05; H, 6.65; N, 9.98 Found%: C, 76.93; H, 6.81; N, 9.97
65	H		2	brown liquid NMR spectrum δ ($CDCl_3$)ppm:1.20-1.50(3H,m),1.60(2H,q,J=7.5Hz),1.66(2H,d,J=11Hz),1.94(2H,t,J=11Hz),2.88(2H,d,J=11Hz),3.27(2H,q,J=7.5Hz),3.49(2H,s),3.79(1H,t,J=7.5Hz),4.06(2H,brs),7.20-7.35(5H,m),7.45(1H,td,J=8,1.5Hz),7.49(1H,td,J=8,1.5Hz),7.74(1H,dd,J=8,1.5Hz),7.89(1H,dd,J=8,1.5Hz) IR spectrum ν (liq.) cm^{-1}:3380 Mass spectrum m/z:394,396(M^+,3:1)

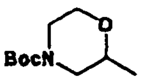
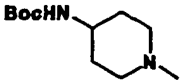
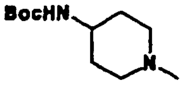


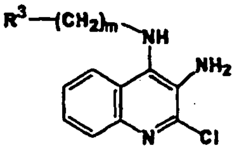
Reference example	B	W	m	Physical properties (Recrystallization solvent)
66	H	CH	0	colorless crystals (AcOEt-iso-Pr_2O) mp,167-167.5℃ Elemental analysis for $C_{18}H_{23}ClN_4O_2$ Calcd.%: C, 60.55; H, 6.69; N, 14.87 Found%: C, 60.47; H, 6.83; N, 14.81
67	Cl	CH	2	colorless crystals (iso-Pr_2O) mp,154-155.5℃ Elemental analysis for $C_{21}H_{28}Cl_2N_4O_2$ Calcd.%: C, 57.40; H, 6.42; N, 12.75 Found%: C, 57.31; H, 6.37; N, 12.69
68	Me	CH	2	colorless crystals (iso-Pr_2O) mp,129-129.5℃ Elemental analysis for $C_{22}H_{31}ClN_4O_2$ Calcd.%: C, 63.07; H, 7.46; N, 13.37 Found%: C, 63.02; H, 7.56; N, 13.33
69	MeO	CH	2	colorless crystals (iso-Pr_2O) mp,140.5-141℃ Elemental analysis for $C_{22}H_{31}ClN_4O_3$ Calcd.%: C, 60.75; H, 7.18; N, 12.88 Found%: C, 60.61; H, 7.17; N, 12.81
70	H	N	2	brown liquid NMR spectrum δ ($CDCl_3$)ppm:1.14(2H,qd,J=12,3Hz),1.40-1.48(11H,m),1.50-1.70(5H,m),2.67(2H,t,J=12Hz),3.40(2H,t,J=7.5Hz),4.07(3H,brs),7.39(1H,dd,J=8.5,4.5Hz),8.29(1H,dd,J=8.5,2Hz),8.91(1H,dd,J=4.5,2Hz) IR spectrum ν (liq.) cm^{-1}:3344,2928,1694 Mass spectrum m/z:405,407(M^+,3:1)

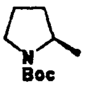
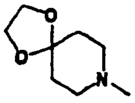
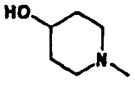
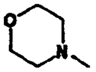
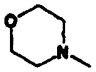


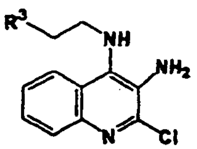
Reference example	R^2	R^3	Physical properties (Recrystallization solvent)
71	Cl		colorless crystals (AcOEt-iso-Pr_2O) mp,115.5-116℃ Elemental analysis for $C_{21}H_{29}ClN_4O_2$ Calcd.%: C, 62.29; H, 7.22; N, 13.84 Found%: C, 61.99; H, 7.28; N, 13.73
72	Me		colorless crystals (iso-Pr_2O) mp,132.5-134.5℃ Elemental analysis for $C_{22}H_{32}N_4O_2$ Calcd.%: C, 68.72; H, 8.39; N, 14.57 Found%: C, 68.65; H, 8.65; N, 14.48
73	Cl		colorless prisms (iso-Pr_2O-n-Heptane) mp,108-110℃ Elemental analysis for $C_{21}H_{29}ClN_4O_2$ Calcd.%: C, 62.29; H, 7.22; N, 13.84 Found%: C, 62.18; H, 7.42; N, 13.81
74	Cl		colorless crystals (iso-Pr_2O) mp,104-106℃ Elemental analysis for $C_{21}H_{29}ClN_4O_2$ Calcd.%: C, 62.29; H, 7.22; N, 13.84 Found%: C, 62.11; H, 7.35; N, 13.79
75	Cl		colorless prisms (AcOEt-iso-Pr_2O) mp,128-128.5℃ Elemental analysis for $C_{20}H_{28}ClN_5O_2$ Calcd.%: C, 59.18; H, 6.95; N, 17.25 Found%: C, 59.16; H, 6.84; N, 17.15

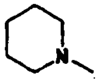
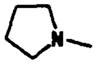


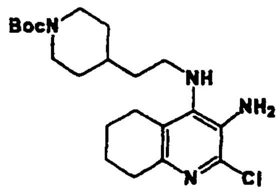
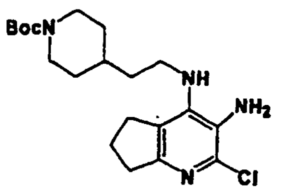
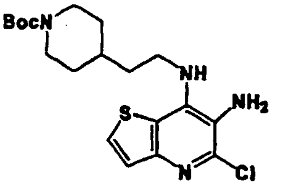
Reference example	R^2	R^3	Physical properties (Recrystallization solvent)
76	Cl		green liquid NMR spectrum δ ($CDCl_3$)ppm:1.47(9H,s),1.78(2H,q,J=6Hz),2.69(1H,brs),2.99(1H,brs),3.30-3.40(1H,m),3.50-3.55(1H,m),3.55-3.70(2H,m),3.75-4.05(3H,m),4.27(2H,brs),7.40-7.50(2H,m),7.80(1H,d,J=7.5Hz),7.90(1H,d,J=7.5Hz) IR spectrum ν (liq.) cm^{-1}:3356,1696 Mass spectrum m/z:406,408(M^+,3:1)
77	Cl		brown liquid NMR spectrum δ ($CDCl_3$)ppm:1.40-1.55(2H,m),1.46(9H,s),2.00-2.05(2H,m),2.15-2.25(2H,m),2.45(2H,t,J=5.5Hz),2.80-2.90(2H,m),3.35(2H,t,J=5.5Hz),3.53(1H,brs),4.34(1H,brs),4.49(1H,brs),7.40-7.50(2H,m),7.85-7.90(2H,m) IR spectrum ν (liq.) cm^{-1}:3356,1694 Mass spectrum m/z:419,421(M^+,3:1)
78	Me		green liquid NMR spectrum δ ($CDCl_3$)ppm:1.40-1.60(2H,m),1.46(9H,s),2.00-2.10(2H,m),2.10-2.25(2H,m),2.46(2H,t,J=5.5Hz),2.64(3H,s),2.85-2.90(2H,m),3.25(2H,t,J=5.5Hz),3.54(1H,brs),4.13(2H,brs),4.49(1H,brs),7.39(1H,t,J=8.5Hz),7.44(1H,t,J=8.5Hz),7.89(1H,d,J=8.5Hz),7.91(1H,d,J=8.5Hz) IR spectrum ν (liq.) cm^{-1}:3352,1704 Mass spectrum m/z:399(M^+)



Reference example	R^3	m	Physical properties (Recrystallization solvent)
79		2	colorless plates (AcOEt-iso-Pr_2O) mp,104-105℃ Elemental analysis for $C_{20}H_{27}ClN_4O_2$ Calcd.%: C, 61.45; H, 6.96; N, 14.33 Found%: C, 61.49; H, 6.81; N, 14.35 Specific rotation $[\alpha]_D^{20}$: -20.9° (c=0.1, DMSO)
80		2	colorless crystals (iso-Pr_2O) mp,96.5-99℃ Elemental analysis for $C_{18}H_{23}ClN_4O_2$ Calcd.%: C, 59.58; H, 6.39; N, 15.44 Found%: C, 59.30; H, 6.67; N, 15.30
81		2	colorless crystals (AcOEt) mp,126-128℃ Elemental analysis for $C_{16}H_{21}ClN_4O$ Calcd.%: C, 59.90; H, 6.60; N, 17.46 Found%: C, 59.71; H, 6.87; N, 17.32
82		2	yellowish brown liquid NMR spectrum δ ($CDCl_3$)ppm:2.49(2H,t,J=5Hz),2.50-2.60(4H,m),3.30-3.40(2H,m),3.75-3.85(4H,m),4.39(1H,brs),4.50(2H,brs),7.44(1H,td,J=8.5,1Hz),7.48(1H,td,J=8.5,1Hz),7.89(1H,dd,J=8.5,1Hz),7.91(1H,dd,J=8.5,1Hz) IR spectrum ν (liq.) cm^{-1}:3348
83		3	yellowish brown liquid NMR spectrum δ ($CDCl_3$)ppm:1.89(2H,quin,J=6Hz),2.45-2.60(4H,m),2.83(2H,t,J=6Hz),3.30(2H,t,J=6Hz),3.78(4H,t,J=4.5Hz),4.50(3H,brs),7.44(1H,td,J=7.5,1Hz),7.47(1H,td,J=7.5,1Hz),7.83(1H,dd,J=7.5,1Hz),7.90(1H,dd,J=7.5,1Hz) IR spectrum ν (liq.) cm^{-1}:3344 Mass spectrum m/z:320,322(M^+, 3:1)



Reference example	R^3	Physical properties
84		greenish brown liquid NMR spectrum δ ($CDCl_3$)ppm:1.45-1.60(2H,m),1.60-1.70(4H,m),2.35-2.60(4H,m),2.39(2H,t,J=5Hz),3.37(2H,t,J=5Hz),4.31(1H,brs),4.67(2H,brs),7.44(1H,td,J=7,1Hz),7.47(1H,td,J=7,1Hz),7.87(1H,dd,J=7,1Hz),7.94(1H,dd,J=7,1Hz) IR spectrum ν (liq.) cm^{-1}:3432,3340 Mass spectrum m/z:304,306(M^+,3:1)
85		dark brown liquid NMR spectrum δ ($CDCl_3$)ppm:1.80-1.90(4H,m),2.57(2H,t,J=5.5Hz),2.60-2.70(4H,m),3.40(2H,t,J=5.5Hz),4.27(3H,brs),7.43(1H,td,J=7.5,2Hz),7.46(1H,td,J=7.5,2Hz),7.87(1H,dd,J=7.5,2Hz),7.93(1H,dd,J=7.5,2Hz) IR spectrum ν (liq.) cm^{-1}:3436,3348 Mass spectrum m/z:290,292(M^+,3:1)

Reference example		Physical properties (Recrystallization solvent)
86		colorless crystals (iso-Pr_2O) mp,130.5-131.5°C Elemental analysis for $C_{21}H_{33}ClN_4O_2$ Calcd.%: C, 61.67; H, 8.13; N, 13.70 Found%: C, 61.52; H, 8.29; N, 13.65
87		colorless crystals ($ClCH_2CH_2Cl$-iso-Pr_2O) mp,141.5-142.5°C Elemental analysis for $C_{20}H_{31}ClN_4O_2$ Calcd.%: C, 60.82; H, 7.91; N, 14.19 Found%: C, 60.63; H, 7.60; N, 14.03
88		gray crystals (AcOEt) mp,168-169°C Elemental analysis for $C_{19}H_{27}ClN_4O_2S$ Calcd.%: C, 55.53; H, 6.62; N, 13.63 Found%: C, 55.54; H, 6.87; N, 13.63

Example 1

4-Chloro-1-[2-(N-triphenylmethyl-4-piperidyl)ethyl]-1H-imidazo[4,5-c]-quinoline

[0091] A solution of 19 9 g of 3-amino-2-chloro-4-[2-(N-triphenylmethyl-4-piperidyl)-ethylamino]quinoline, 24.1 ml of ethyl orthoformate and 0.68 g of p-toluenesulfonic acid monohydrate in 200 ml of toluene was refluxed for 6 hours. After cooling, the precipitated crystals were collected by filtration, and washed with diisopropyl ether to give 16.4 g of colorless crystals. Recrystallization from a mixture of methanol and tetrahydrofuran gave colorless crystals having the melting point of from 229 to 234.5°C (decomposition).

Elemental analysis for $C_{38}H_{33}ClN_4$			
Calculated %	C, 77.61;	H, 5.97;	N, 10.06
Found %	C, 77.50;	H, 5.98;	N, 9.95

Example 2

4-Chloro-2-trifluoromethyl-1-[2-(N-triphenylmethyl-4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline

[0092] To a solution of 2.50 g of 3-amino-2-chloro-4-[2-(N-triphenylmethyl-4-piperidyl)ethylamino]quinoline and 0 76 ml of triethylamine in 60 ml of dried tetrahydrofuran, a solution of 0.63 ml of trifluoroacetic anhydride in 40 ml of dried tetrahydrofuran was added dropwise under ice-cooling, and the mixture was stirred at room temperature for 2 hours. The solvent of the reaction mixture was evaporated, and the residue was added with water and saturated aqueous sodium hydrogencarbonate solution, and extracted with ethyl acetate. The extract was washed successively with water and saturated brine, and dried, and then the solvent was evaporated. A solution of 3.03 g of the resulting pale yellow solid and 0.30 g of p-toluenesulfonic acid monohydrate in 100 ml of toluene was refluxed for 20 hours. After the reaction, the solvent was evaporated, and the residue was added with methanol and acetone. The precipitated crystals were collected by filtration to give 1 79 g of colorless crystals.

NMR spectrum δ (DMSO-d_6)ppm : 1.35-1.55(3H,m),1.59(2H,q,J=11Hz),1.77(2H,d,J=11Hz),1.80-1 90(2H,m),2.98(2H, brs),4 75(2H,t,J=8.5Hz),7.17(3H,t,J=8Hz),7.30(6H,t,J=8Hz),7.41(6H,brs),7.84(1H,td,J=7.5,2Hz),7 87(1H,td, J=7.5,2Hz),8.16(1H,dd,J=7.5,2Hz),8.34(1H,dd,J=7.5,2Hz)

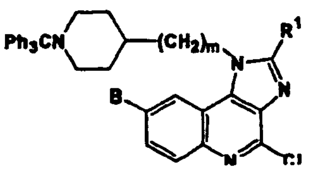
Example 3

tert-Butyl 4-[2-(4-methyl-2 -phenyl-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]-1-piperidinecarboxylate

[0093] A solution of 0.65 g of tert-butyl 4-[2-[(3-amino-2-methylquinolin-4-yl)amino]-ethyl]-1-piperidinecarboxylate, 0.29 g of benzaldehyde and 0.08 g of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in 5 ml of tetrahydrofuran was stirred at room temperature for 3 days. The reaction mixture was added with saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed successively with saturated aqueous sodium hydrogencarbonate solution and saturated brine, and dried, and the solvent was evaporated to give a reddish brown liquid. The resulting liquid was purified by silica gel column chromatography using ethyl acetate - n-heptane (1:1) as an eluting solvent, and washed with diisopropyl ether to give 0.55 g of a colorless solid. Recrystallization from diisopropyl ether gave colorless crystals having the melting point of from 146 to 146.5°C.

Elemental analysis for $C_{29}H_{34}N_4O_2$			
Calculated %	C, 74.01;	H, 7 28;	N, 11.91
Found %	C, 73.95;	H, 7.54;	N, 11.84

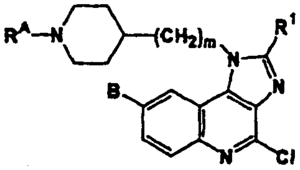
[0094] In accordance with the methods of Examples 1 through 3, the compounds of Examples 4 through 72 were obtained.



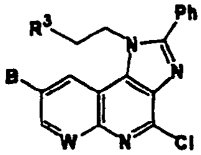
Example	R¹	B	m	Physical properties (Recrystallization solvent)
4	H	H	1	colorless crystals (MeOH) mp,232-239°C (decomposition) Elemental analysis for $C_{35}H_{31}ClN_4$ Calcd.%: C, 77.40; H, 5.75; N, 10.32 Found%: C, 77.35; H, 5.79; N, 10.19
5	Ph	H	1	pale yellow crystals (AcOEt) mp,165-168°C (decomposition) Elemental analysis for $C_{41}H_{35}ClN_4$ Calcd.%: C, 79.53; H, 5.70; N, 9.05 Found%: G, 79.29; H, 5.74; N, 9.05
6	H	Cl	2	colorless crystals (MeOH) mp,266-268°C (decomposition) Elemental analysis for $C_{36}H_{32}Cl_2N_4$ Calcd.%: C, 73.09; H, 5.45; N, 9.47 Found%: C, 73.15; H, 5.54; N, 9.41

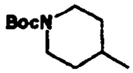
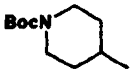
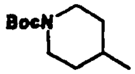
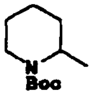
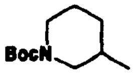
(continued)

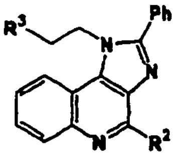
Example	R^1	B	m	Physical properties (Recrystallization solvent)
7	Ph	H	2	pale yellow crystals (CH_2Cl_2-EtOH) mp,246.5-249°C Elemental analysis for $C_{42}H_{37}ClN_4$ Calcd.%: C, 79.66; H, 5.89; N, 8.85 Found%: C, 79.55; H, 6.12; N, 8.71
8	Ph	H	3	colorless crystals (AcOEt) mp,227.5-231°C (decomposition) Elemental analysis for $C_{43}H_{39}ClN_4$-1/4H_2O Calcd.%: C, 79.24; H, 6.11; N, 8.60 Found%: C, 79.26; H, 6.09; N, 8.55

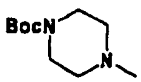
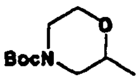
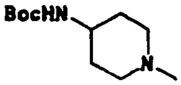
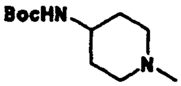


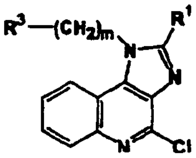
Example	R^1	B	R^A	m	Physical properties (Recrystallization solvent)
9	H	H	Bn	2	colorless crystals (AcOEt) mp,124.5-125°C Elemental analysis for $C_{24}H_{25}ClN_4$ Calcd.%: C, 71.19; H, 6.22; N, 13.84 Found%: C, 71.22; H, 5.97; N, 13.79
10	Ph	H	Boc	0	colorless crystals (AcOEt-MeOH) mp,250-255°C (decomposition) Elemental analysis for $C_{26}H_{27}ClN_4O_2$ Calcd.%: C, 67.45; H, 5.88; N, 12.10 Found%: C, 67.42; H, 5.88; N, 12.02
11	H	H	Boc	2	colorless crystals (AcOEt) mp,188-189°C Elemental analysis for $C_{22}H_{27}ClN_4O_2$ Calcd.%: C, 63.68; H, 6.56; N, 13.50 Found%: C, 63.45; H, 6.60: N, 13.40
12	Ph	Cl	Boc	2	colorless crystals (AcOEt) mp,192-193°C Elemental analysis for $C_{28}H_{30}Cl_2N_4O_2$ Calcd.%: C, 64.00; H, 5.75; N, 10.66 Found%: C, 64.04; H, 5.59; N, 10.61
13	Ph	Me	Boc	2	colorless crystals (AcOEt) mp,182.5-183.5°C Elemental analysis for $C_{29}H_{33}ClN_4O_2$ Calcd.%: C, 68.97; H, 6.59; N, 11.09 Found%: C, 68.91; H, 6.41; N, 11.06

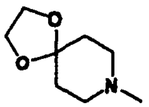
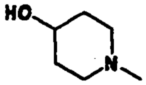
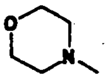
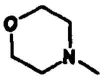
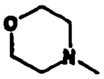


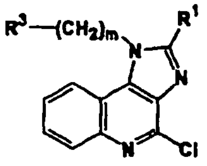
Example	B	R^3	W	Physical properties (Recrystallization solvent)
14	MeO		CH	colorless crystals (AcOEt) mp,188.5-189.5℃ Elemental analysis for $C_{29}H_{33}ClN_4O_3$ Calcd.%: C, 66.85; H, 6.38; N, 10.75 Found%: C, 66.70; H, 6.42; N, 10.70
15	H		N	colorless crystals (MeOH) mp,225.5-227.5℃(decomposition) Elemental analysis for $C_{27}H_{30}ClN_5O_2$ Calcd.%: C, 65.91; H, 6.15; N, 14.23 Found%: C, 65.85; H, 6.21; N, 14.21
16	H		CH	colorless crystals(AcOEt-n-Heptane) mp,159-161℃ Elemental analysis for $C_{29}H_{31}ClN_4O_2$ Calcd.%: C, 68.49; H, 6.36; N, 11.41 Found%: C, 68.36; H, 6.27; N, 11.37
17	H		CH	colorless crystals (AcOEt-iso-Pr_2O) mp,154.5-156℃ Elemental analysis for $C_{29}H_{31}ClN_4O_2$ Calcd.%: C, 68.49; H, 6.36; N, 11.41 Found%: C, 68.59; H, 6.15; N, 11.38
18	H		CH	colorless crystals (AcOEt) mp,166.5-167.5℃ Elemental analysis for $C_{29}H_{31}ClN_4O_2$ Calcd.%: C, 68.49; H, 6.38; N, 11.41 Found%: C, 68.50; H, 6.43; N, 11.32

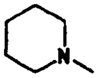
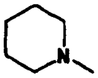
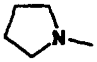
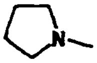


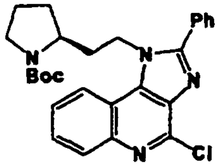
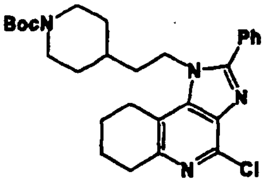
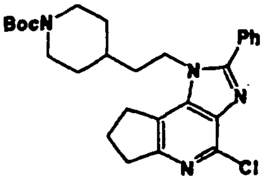
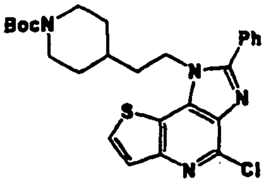
Example	R^2	R^3	Physical properties (Recrystallization solvent)
19	Cl		colorless fine needles(AcOEt) mp,186.5-187.5℃ Elemental analysis for $C_{27}H_{30}ClN_5O_2$ Calcd.%: C, 65.91; H, 6.15; N, 14.23 Found%: C, 65.97; H, 6.31; N, 14.18
20	Cl		colorless crystals (MeOH) mp,195.5-196.5℃ Elemental analysis for $C_{27}H_{29}ClN_4O_3$ Calcd.%: C, 65.78; H, 5.93; N, 11.36 Found%: C, 65.73; H, 5.86; N, 11.38
21	Cl		colorless crystals (AcOEt-iso-Pr_2O) mp,191.5-192℃ Elemental analysis for $C_{28}H_{32}ClN_5O_2$ Calcd.%: C, 66.46; H, 6.37; N, 13.84 Found%: C, 66.42; H, 6.33; N, 13.69
22	Me		colorless crystals (AcOEt-iso-Pr_2O) mp,164.5-165℃ Elemental analysis for $C_{29}H_{35}N_5O_2$ Calcd.%: C, 71.72; H, 7.26; N, 14.42 Found%: C, 71.40; H, 7.24; N, 14.28

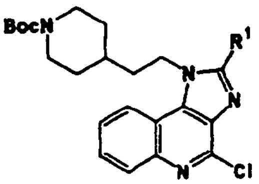


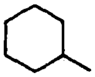
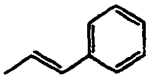
Example	R^1	R^3	m	Physical properties (Recrystallization solvent)
23	Ph		2	colorless crystals (AcOEt-iso-Pr_2O) mp,185-188°C Elemental analysis for $C_{25}H_{25}ClN_4O_2$ Calcd.%: C, 66.88; H, 5.61; N, 12.48 Found%: C, 66.59; H, 5.63; N, 12.45
24	Ph		2	colorless crystals (iso-PrOH) mp,164-170°C Elemental analysis for $C_{23}H_{23}ClN_4O$ Calcd.%: C, 67.89; H, 5.70; N, 13.77 Found%: C, 67.62; H, 5.71; N, 13.63
25	Ph		2	pale yellowish brown crystals (AcOEt) mp,182-183°C Elemental analysis for $C_{22}H_{21}ClN_4O \cdot 1/4H_2O$ Calcd.%: C, 66.49; H, 5.45; N, 14.10 Found%: C, 66.26; H, 5.50; N, 14.03
26	H		3	pale brown crystals (AcOEt) mp,130.5-131.5°C Elemental analysis for $C_{17}H_{19}ClN_4O$ Calcd.%: C, 61.72; H, 5.79; N, 16.94 Found%: C, 61.72; H, 5.76; N, 16.90
27	Ph		3	pale brown crystals (MeOH) mp,183.5-184.5°C Elemental analysis for $C_{23}H_{23}ClN_4O$ Calcd.%: C, 67.89; H, 5.70; N, 13.77 Found%: C, 67.91; H, 5.66; N, 13.80

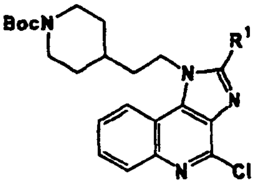


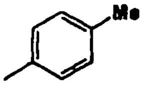
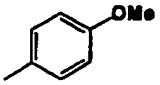
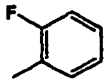
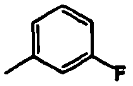
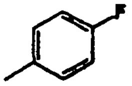
Example	R^1	R^3	m	Physical propertie (Recrystallization solvent)
28	H		2	pale brown crystals (iso-Pr_2O) mp,105-105.5℃ Elemental analysis for $C_{17}H_{18}ClN_4$ Calcd.%: C, 64.88; H, 6.08; N, 17.80 Found%: C, 64.83; H, 6.11; N, 17.72
29	Ph		2	pale brown crystals (MeOH) mp,226-227℃ Elemental analysis for $C_{23}H_{23}ClN_4$ Calcd.%: C, 70.67; H, 5.93; N, 14.33 Found%: C, 70.44; H, 5.96; N, 14.29
30	H		2	brown crystals NMR spectrum δ($CDCl_3$)ppm:1.80-1.90(4H,m),2.58-2.76(4H,m),3.14-3.22(2H,m),4.78-4.91(2H,m),7.68(1H,t,J=6.5Hz),7.72(1H,t,J=6.5Hz),8.13(1H,s),8.22(2H,d,J=6.5Hz) Mass spectrum m/z:300,302(M^+,3:1)
31	Ph		2	pale brown crystals (MeOH) mp,191-192℃ Elemental analysis for $C_{22}H_{21}ClN_4$ Calcd.%: C, 70.11; H, 5.62; N, 14.87 Found%: C, 70.00; H, 5.65; N, 14.86

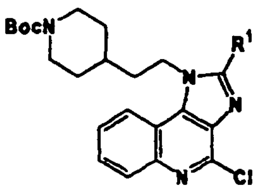
Example		Physical properties (Recrystallization solvent)
32		colorless amorphous solid NMR spectrum δ (DMSO-d_6)ppm:0.99(3H,brs),1.32(3H,brs),1.68(2H,brs),2.13(1H,brs),2.49(9H,s),4.62-4.72(2H,m),7.60-7.67(3H,m),7.74-7.82(4H,m),8.13(1H,dd,J=8,1.5Hz),8.42(1H,d,J=8Hz) IR spectrum ν (KBr)cm^{-1}:1690 Mass spectrum m/z:476,478(M^+,3:1) Specific rotation $[\alpha]_D^{20}$: -60.2° (c=0.1, DMSO)
33		colorless crystals (AcOEt) mp,215-218℃ (decomposition) Elemental analysis for $C_{28}H_{35}ClN_4O_2$ Calcd.%: C, 67.93; H, 7.13; N, 11.32 Found%: C, 67.70; H, 7.17; N, 11.23
34		colorless crystals (MeOH-iso-PrOH) mp,185-188℃ Elemental analysis for $C_{27}H_{33}ClN_4O_2$ Calcd.%: C, 67.42; H, 6.91; N, 11.65 Found%: C, 67.31; H, 6.66; N, 11.57
35		brown crystals (AcOEt) mp,199-200℃ Elemental analysis for $C_{26}H_{29}ClN_4O_2S$ Calcd.%: C, 62.83; H, 5.88; N, 11.27 Found%: C, 62.74; H, 5.83; N, 11.16

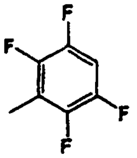
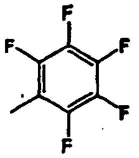
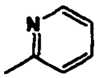
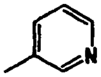
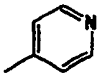


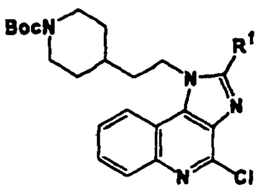
Example	R^1	Physical properties (Recrystallization solvent)
36	Me	pale brown crystals (iso-PrOH) mp,202-203℃ Elemental analysis for $C_{23}H_{29}ClN_4O_2$ Calcd.%: C, 64.40; H, 6.81; N, 13.06 Found%: C, 64.39; H, 7.04; N, 12.95
37	n-Bu	colorless crystals (AcOEt-iso-Pr_2O) mp,159.5-160.5℃ Elemental analysis for $C_{26}H_{35}ClN_4O_2$ Calcd.%: C, 66.30; H, 7.49; N, 11.89 Found%: C, 66.16; H, 7.53; N, 11.82
38		colorless crystals (iso-PrOH) mp,174-175℃ Elemental analysis for $C_{28}H_{37}ClN_4O_2 \cdot 1/4H_2O$ Calcd.%: C, 67.05; H, 7.54; N, 11.17 Found%: C, 67.08; H, 7.47; N, 10.92
39	Bn	colorless crystals (AcOEt-iso-Pr_2O) mp,165-166.5℃ Elemental analysis for $C_{29}H_{33}ClN_4O_2$ Calcd.%: C, 68.97; H, 6.59; N, 11.09 Found%: C, 68.93; H, 6.72; N, 10.99
40		colorless crystals (AcOEt) mp,219-220.5℃(decomposition) Elemental analysis for $C_{30}H_{33}ClN_4O_2 \cdot 1/4H_2O$ Calcd.%: C, 69.08; H, 6.47; N, 10.74 Found%: C, 69.25; H, 6.41; N, 10.69

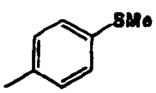
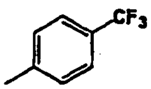
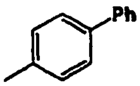
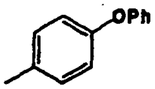
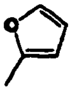


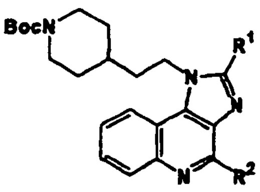
Example	R^1	Physical properties (Recrystallization solvent)
41		colorless crystals (MeOH) mp,137-142℃ Elemental analysis for $C_{29}H_{33}ClN_4O_2 \cdot 1/2H_2O$ Calcd.%: C, 67.76; H, 6.67; N, 10.90 Found%: C, 67.82; H, 6.49; N, 10.92
42		colorless crystals (MeOH) mp,153.5-157℃ Elemental analysis for $C_{29}H_{33}ClN_4O_3$ Calcd.%: C, 66.85; H, 6.38; N, 10.75 Found%: C, 66.84; H, 6.54; N, 10.78
43		colorless crystals (AcOEt) mp,160-161℃ Elemental analysis for $C_{28}H_{30}ClFN_4O_2 \cdot 1/8H_2O$ Calcd.%: C, 65.78; H, 5.96; N, 10.96 Found%: C, 65.57; H, 5.87; N, 10.94
44		colorless fine needles (AcOEt-n-Heptane) mp,180-182℃ Elemental analysis for $C_{28}H_{30}ClFN_4O_2$ Calcd.%: C, 66.07; H, 5.94; N, 11.01 Found%: C, 66.10; H, 5.71; N, 11.06
45		colorless crystals (AcOEt-iso-Pr$_2$O) mp,126-129.5℃ Elemental analysis for $C_{28}H_{30}ClFN_4O_2$ Calcd.%: C, 66.07; H, 5.94; N, 11.01 Found%: C, 66.08; H, 5.76; N, 11.01

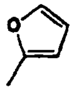
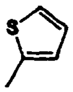
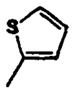
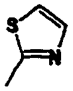
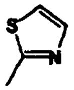


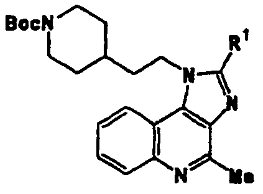
Example	R^1	Physical properties (Recrystallization solvent)
46		colorless crystals (iso-PrOH) mp,199.5-200℃ Elemental analysis for $C_{28}H_{27}ClF_4N_4O_2$ Calcd.%: C, 59.74; H, 4.83; N, 9.95 Found%: C, 59.61; H, 4.89; N, 9.90
47		colorless crystals (iso-PrOH) mp,216.5-217.5℃ Elemental analysis for $C_{28}H_{26}ClF_5N_4O_2$ Calcd.%: C, 57.89; H, 4.51; N, 9.64 Found%: C, 57.88; H, 4.56; N, 9.62
48		colorless crystals (AcOEt) mp,199.5-200.5℃ Elemental analysis for $C_{27}H_{30}ClN_5O_2$ Calcd.%: C, 65.91; H, 6.15; N, 14.23 Found%: C, 65.77; H, 5.99; N, 14.25
49		colorless prisms (AcOEt-n-Heptane) mp,182-183℃ Elemental analysis for $C_{27}H_{30}ClN_5O_2$ Calcd.%: C, 65.91; H, 6.15; N, 14.23 Found%: C, 65.95; H, 6.26; N, 14.24
50		colorless prisms(AcOEt) mp,213-214℃ Elemental analysis for $C_{27}H_{30}ClN_5O_2$ Calcd.%: C, 65.91; H, 6.15; N, 14.23 Found%: C, 65.87; H, 6.20; N, 14.23

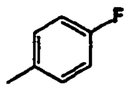
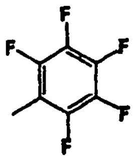
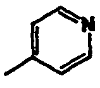
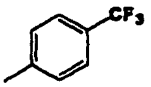
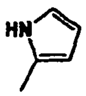


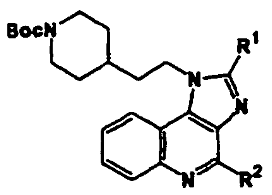
Example	R^1	Physical properties (R crystallization solvent)
51		colorless crystals (MeOH) mp,179-186°C Elemental analysis for $C_{29}H_{33}ClN_4O_2S$ Calcd.%: C, 64.85; H, 6.19; N, 10.43 Found%: C, 64.82; H, 6.45; N, 10.37
52		colorless crystals (iso-PrOH) mp,203-203.5°C Elemental analysis for $C_{29}H_{30}ClF_3N_4O_2$ Calcd.%: C, 62.31; H, 5.41; N, 10.02 Found%: C, 62.24; H, 5.42; N, 9.99
53		colorless crystals (AcOEt) mp,224-225°C Elemental analysis for $C_{34}H_{35}ClN_4O_2$ Calcd.%: C, 72.01; H, 6.22; N, 9.88 Found%: C, 72.02; H, 6.21; N, 9.92
54		colorless crystals (iso-PrOH) mp,197-198°C Elemental analysis for $C_{34}H_{35}ClN_4O_3$ Calcd.%: C, 70.03; H, 6.05; N, 9.61 Found%: C, 69.83; H, 6.08; N, 9.58
55		colorless crystals (MeOH) mp,196.5-197°C Elemental analysis for $C_{26}H_{29}ClN_4O_3$ Calcd.%: C, 64.93; H, 6.08; N, 11.65 Found%: C, 64.83; H, 6.27; N, 11.69

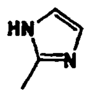
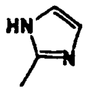
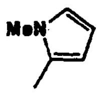


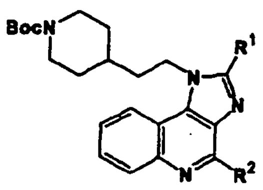
Example	R¹	R²	Physical properties (Recrystallization solvent)
56		Me	pale yellow crystals (iso-PrOH) mp,185.5-186℃ Elemental analysis for $C_{27}H_{32}N_4O_3$ Calcd.%: C, 70.41; H, 7.00; N, 12.16 Found%: C, 70.32; H, 7.19; N, 12.13
57		Cl	colorless crystals (MeOH) mp,151.5-153℃ Elemental analysis for $C_{26}H_{29}ClN_4O_2S$ Calcd.%: C, 62.83; H, 5.88; N, 11.27 Found%: C, 62.77; H, 6.01; N, 11.24
58		Me	pale yellow crystals (iso-PrOH) mp,181.5-182.5℃ Elemental analysis for $C_{27}H_{32}N_4O_2S$ Calcd.%: C, 68.04; H, 6.77; N, 11.75 Found%: C, 67.86; H, 6.99; N, 11.63
59		Cl	colorless crystals (AcOEt) mp,197-198℃ Elemental analysis for $C_{25}H_{28}ClN_5O_2S$ Calcd.%: C, 60.29; H, 5.67; N, 14.06 Found%: C, 59.98; H, 5.54; N, 13.84
60		Me	colorless crystals (AcOEt-iso-Pr$_2$O) mp,191-193℃ Elemental analysis for $C_{26}H_{31}N_5O_2S$ Calcd.%: C, 65.38; H, 6.54; N, 14.66 Found%: C, 65.34; H, 6.53; N, 14.43

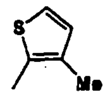
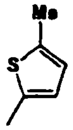
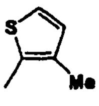
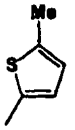


Example	R^1	Physical properties (Recrystallization solvent)
61		yellow amorphous solid NMR spectrum δ ($CDCl_3$)ppm: 1.06-1.09(2H,m),1.30-1.40(1H,m),140-1.45 (2H,m) ,1.44(9H,s),1.82-1.90(2H,m),2.55-2.62(2H,m),3.05(3H,s),4.00-4.10(2H,m),4.62(2H,t,J=7.5Hz),7.27-7.30(2H,m),7.61(1H,t,J=7Hz),7.67-7.71(3H,m),8.14(1H,d,J=7.5Hz),8.24(1H,d,J=7.5Hz) IR spectrum ν (KBr)cm^{-1}:1692 Mass spectrum m/z:488(M^+)
62		colorless crystals (AcOEt) mp,195-196℃ Elemental analysis for $C_{29}H_{29}F_5N_4O_2$ Calcd.%: C, 62.14; H, 5.21; N, 9.99 Found%: C, 62.07; H, 5.25; N, 9.94
63		pale yellow crystals (AcOEt) mp,199.5-200.5℃ Elemental analysis for $C_{28}H_{33}N_5O_2$ Calcd.%: C, 71.31; H, 7.05; N, 14.85 Found%: C, 71.37; H, 7.14; N, 14.83
64		colorless crystals (MeOH-iso-Pr_2O) mp,177.5-179℃ Elemental analysis for $C_{30}H_{33}F_3N_4O_2$ Calcd.%: C, 66.90; H, 6.18; N, 10.40 Found%: C, 66.89; H, 6.08; N, 10.37
65		pale brown crystals (AcOEt) mp,193-194℃ Elemental analysis for $C_{27}H_{33}N_5O_2$ Calcd.%: C, 70.56; H, 7.24; N, 15.24 Found%: C, 70.61; H, 7.16; N, 15.21



Example	R^1	R^2	Physical properties (Recrystallization solvent)
66		Cl	colorless crystals (EtOH) mp.240-241℃ (decomposition) Elemental analysis for $C_{25}H_{29}ClN_6O_2$ Calcd.%: C, 62.43; H, 6.08; N, 17.47 Found%: C, 62.49; H, 6.02; N, 17.51
67		Me	colorless crystals (EtOH) mp.228.5-230℃ (decomposition) Elemental analysis for $C_{26}H_{32}N_6O_2$ Calcd.%: C, 67.80; H, 7.00; N, 18.25 Found%: C, 67.72; H, 6.93; N, 18.24
68		Me	brown amorphous solid NMR spectrum δ ($CDCl_3$)ppm:1.10-1.20(2H,m),1.48(9H,s),1.40-1.60(3H,m),1.90-1.98(2H,m),2.60-2.70(2H,m),3.04(3H,s),3.86(3H,s),4.05-4.15(2H,m),4.74(2H,t,J=8Hz),6.30(1H,t,J=2.5Hz),6.52(1H,d,J=2.5Hz),6.88(1H,s),7.60(1H,t,J=8Hz),7.67(1H,t,J=8Hz),8.16(1H,d,J=8Hz),8.23(1H,d,J=8Hz) IR spectrum ν (KBr)cm^{-1}:1688 Mass spectrum m/z:473(M^+)



Example	R¹	R²	Physical properties (Recrystallization solvent)
69		Cl	yellow amorphous solid NMR spectrum δ ($CDCl_3$)ppm: 1.05–1.15(2H,m),1.40–1.50(3H,m),1.45(9H,s),1.83–1.90(2H,m),2.32(3H,s),2.60–2.70(2H,m),4.00–4.10(2H,m),4.60–4.65(2H,m),7.06(1H,d,J=5.5Hz),7.51(1H,d,J=5.5Hz),7.68–7.75(2H,m),8.16(1H,d,J=7.5Hz),8.24(1H,d,J=7.5Hz)
70		Cl	pale yellow crystals (EtOH) mp,192–193℃ Elemental analysis for $C_{27}H_{31}ClN_4O_2S \cdot 5/4H_2O$ Calcd.%: C, 60.77; H, 6.33; N, 10.50 Found%: C, 60.82; H, 6.08; N, 10.17
71		Me	yellow amorphous solid NMR spectrum δ ($CDCl_3$)ppm: 1.02–1.08(2H,m),1.44(9H,s),1.44–1.50(3H,m),1.80–1.90(2H,m),2.31(3H,s),2.60–2.70(2H,m),3.05(3H,s),4.00–4.05(2H,m),4.59(2H,t,J=7.5Hz),7.06(1H,d,J=5.5Hz),7.49(1H,d,J=5.5Hz),7.60–7.65(2H,m),8.14(1H,d,J=8Hz),8.23(1H,d,J=8Hz) IR spectrum ν (KBr)cm⁻¹:1688 Mass spectrum m/z:490(M⁺)
72		Me	pale yellow crystals (AcOEt) mp,141–142℃ Elemental analysis for $C_{28}H_{34}N_4O_2S \cdot 1/4H_2O$ Calcd.%: C, 67.92; H, 7.02; N, 11.31 Found%: C, 67.86; H, 6.84; N, 11.25

Example 73

tert-Butyl 4-[2-(4-chloro-2-hydroxy-1H-imidazo[4,5-c]quinolin-1-yl)-ethyl]-1-piperidinecarboxylate

[0095] To a solution of 0 60 g of tert-butyl 4-(2-(3-amino-2-chloro-4-quinolylamino)-ethyl]-1-piperidinecarboxylate and 0.44 g of triphosgene in 10 ml of 1,2-dichloroethane, 0.41 ml of triethylamine was added dropwise, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was neutralized with saturated aqueous sodium hydrogencarbonate solution, and extracted with 1,2-dichloroethane. The extract was washed with saturated brine, and dried, and the solvent was evaporated. The residue was washed with diisopropyl ether to give 0.57 g of colorless crystals. Recrystallization from 1,2-dichloroethane gave colorless crystals having the melting point of from 222 to 223°C

Elemental analysis for $C_{22}H_{27}ClN_4O_3$			
Calculated % Found %	C, 61.32; C, 61.15;	H, 6.32; H, 6.34;	N, 13.00 N, 13.00

Example 74

tert-Butyl 4-[2-[4-chloro-2-(4-methanesulfinylphenyl)-1H-imidazo[4,5-c]-quinolin-1-yl]ethyl]-1-piperidinecarboxylate

[0096] To a suspension of 0.63 g of tert-butyl 4-[2-[4-chloro-2-(4-methylthio-phenyl)-1H-imidazo[4,5-c]quinolin-1-yl] ethyl]-1-piperidinecarboxylate in 18 ml of 1,4-dioxane, a solution of 0.38 g of sodium periodate in 6 ml of water was added dropwise, and the mixture was stirred at 50°C for 13 hours. The reaction solution was concentrated, and the residue was purified by silica gel column chromatography using 1,2-dichloroethane - methanol (10:1) as an eluting solvent to give 0 47 g of a colorless solid. Recrystallization from a mixture of isopropanol and water gave colorless crystals having the melting point of from 183 to 186°C.

Elemental analysis for $C_{29}H_{33}ClN_4O_3S \cdot 1/4H_2O$			
Calculated %	C, 62.46;	H, 6.06;	N, 10.05
Found %	C, 62.33;	H, 5.90;	N, 9.91

Example 75

tert-Butyl 4-[2-[4-chloro-2-(4-methanesulfonylphenyl)-1H-imidazo[4,5-c]-quinolin-1-yl]ethyl]-1-piperidinecarboxylate

[0097] To a solution of 0 40 g of tert-butyl 4-[2-[4-chloro-2-(4-methylthiophenyl)-1H-imidazo[4,5 -c]quinolin-1-yl] ethyl]-1-piperidinecarboxylate in 20 ml of 1,2-dichloroethane, 0.40 g of m-chloroperbenzoic acid was added portionwise little by little, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was neutralized with 10% aqueous sodium hydroxide solution, and extracted with 1,2-dichloroethane. The extract was washed with saturated aqueous sodium hydrogencarbonate solution and dried, and then the solvent was evaporated. The residue was washed with a mixture of diisopropyl ether and diethyl ether to give 0.42 g of colorless crystals. Recrystallization from methanol gave colorless crystals having the melting point of from 149 to 156°C.

Elemental analysis for $C_{29}H_{33}ClN_4O_4S \cdot 1/4H_2O$			
Calculated %	C, 60.72;	H, 5.89;	N, 9.77
Found %	C, 60.72;	H, 5.81;	N, 9.67

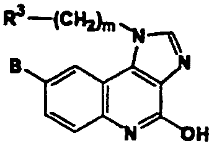
Example 76

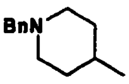
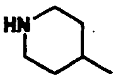
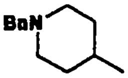
4-Hydroxy-2-phenyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline

[0098] A solution of 871 mg of 4-chloro-2-phenyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline and 2.5 ml of 6 N hydrochloric acid in 8 ml of 1,4-dioxane was refluxed for 3 hours. The reaction mixture was adjusted to pH 10 with 10% aqueous sodium hydroxide solution, and added with potassium carbonate, and then extracted with 1,2-dichloroethane. The extract was dried, and the solvent was evaporated. The resulting residue was washed with ethyl acetate to give 522 mg of pale brown crystals. Recrystallization from methanol gave pale brown crystals having the melting point of from 242.5 to 244°C.

Elemental analysis for $C_{23}H_{24}N_4O \cdot 1/4H_2O$			
Calculated %	C, 73.28;	H, 6.55;	N, 14.86
Found %	C, 73.32;	H, 6.45;	N, 14.77

[0099] In accordance with the method of Example 76, the compounds of Examples 77 through 79 were obtained.



Example	B	R^3	m	Physical properties (Recrystallization solvent)
77	Cl		2	colorless crystals (MeOH) mp,269-280℃ (decomposition) Elemental analysis for $C_{24}H_{25}ClN_4O$ Calcd.%: C, 68.48; H, 5.99; N, 13.31 Found%: C, 68.32; H, 6.07; N, 13.29
78	H		1	colorless crystals [hydrochloride] NMR spectrum δ (DMSO-d_6)ppm: 1.56(2H,q,J=11.5Hz),1.74(2H,d,J=11.5Hz),2.10-2.25(1H,m),2.79(2H,q,J=11.5Hz),3.24(2H,d,J=11.5Hz),4.54(2H,d,J=7.5Hz),7.29(1H,t,J=8Hz),7.49(1H,d,J=8Hz),7.50(1H,t,J=8Hz),8.00(1H,d,J=8Hz),8.38(1H,s),8.84(1H,brs),8.95(1H,brs),11.62(1H,s) IR spectrum ν (KBr) cm^{-1}:3544,3228,1692 Mass spectrum m/z:282(M^+)
79	H		1	colorless crystals [hydrochloride] NMR spectrum δ (DMSO-d_6)ppm: 1.65-1.85(4H,m),2.00-2.15(1H,m),2.84(2H,q,J=12Hz),3.30(2H,d,J=12Hz),4.18(2H,d,J=5Hz),4.51(2H,d,J=7.5Hz),7.27(1H,t,J=6.5Hz),7.40-7.60(7H,m),7.97(1H,d,J=8Hz),8.31(1H,s),10.63(1H,brs),11.58(1H,s) IR spectrum ν (KBr) cm^{-1}:3416,1672 Mass spectrum m/z:372(M^+)

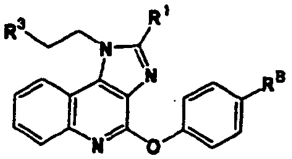
Example 80

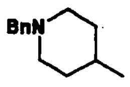
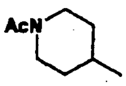
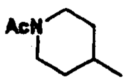
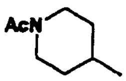
tert-Butyl 4-[2-(4-phenoxy-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]-1-piperidinecarboxylate

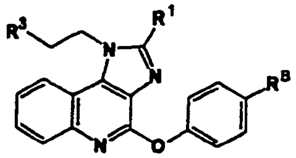
[0100] A mixture of 4.46 g of tert-butyl 4-[2-(4-chloro-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]-1-piperidinecarboxylate, 10.1 g of phenol and 1.80 g of potassium hydroxide was stirred at 120°C for 7 hours. The reaction mixture was adjusted to pH 10 with 10% aqueous sodium hydroxide solution, and extracted with ethyl acetate. The extract was washed successively with 10% aqueous sodium hydroxide solution and saturated brine, and dried, and then the solvent was evaporated to give a brown liquid. The resulting brown liquid was purified by silica gel column chromatography using ethyl acetate as an eluting solvent to give 3.59 g of a colorless solid. Recrystallization from a mixture of ethyl acetate and n-hexane gave colorless crystals having the melting point of from 130.5 to 132.5°C.

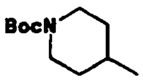
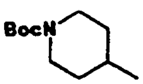
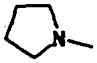
Elemental analysis for $C_{28}H_{32}N_4O_3$			
Calculated % Found %	C, 71.16; C, 71.10;	H, 6.83; H, 7.10;	N, 11.86 N, 11.69

[0101] In accordance with the method of Example 80, the compounds of Examples 81 through 87 were obtained.



Example	R^1	R^3	R^8	Physical properties (Recrystallization solvent)
81	H		H	colorless crystals (MeOH) mp,152.5-153.5℃ Elemental analysis for $C_{30}H_{30}N_4O$ Calcd.%: C, 77.89; H, 6.54; N, 12.11 Found%: C, 78.00; H, 6.29; N, 12.05
82	H		H	colorless crystals (AcOEt-iso-Pr_2O) mp,187-189.5℃ Elemental analysis for $C_{25}H_{26}N_4O_2$ Calcd.%: C, 72.44; H, 6.32; N, 13.52 Found%: C, 72.35; H, 6.26; N, 13.42
83	H		F	colorless crystals (CH_2Cl_2-iso-Pr_2O) mp,206.5-208℃ Elemental analysis for $C_{25}H_{25}FN_4O_2 \cdot 1/8H_2O$ Calcd.%: C, 69.07; H, 5.85; N, 12.89 Found%: C, 69.11; H, 5.74; N, 12.85
84	Ph		H	colorless crystals (MeOH-iso-Pr_2O) mp,205-207.5℃ Elemental analysis for $C_{31}H_{30}N_4O_2 \cdot 1/2H_2O$ Calcd.%: C, 74.53; H, 6.25; N, 11.21 Found%: C, 74.52; H, 6.37; N, 11.10



Example	R^1	R^3	R^8	Physical properties (Recrystallization solvent)
85	H		F	colorless crystals (AcOEt-n-Hexane) mp,133.5-135.5℃ Elemental analysis for $C_{28}H_{31}FN_4O_3$ Calcd.%: C, 68.55; H, 6.37; N, 11.42 Found%: C, 68.37; H, 6.47; N, 11.25
86	Ph		H	colorless crystals (iso-PrOH) mp,207-208℃ Elemental analysis for $C_{34}H_{36}N_4O_3$ Calcd.%: C, 74.43; H, 6.61; N, 10.21 Found%: C, 74.38; H, 6.68; N, 10.14
87	H		H	pale purple crystals NMR spectrum δ (DMSO-d_6)ppm: 1.64-1.72(4H,m),2.55-2.58(4H,m),2.98(2H,t,J=7 Hz),4.80(2H,t,J=7Hz),7.25-7.31(3H,m),7.45-7.49(2H,m),7.53-7.60(2H,m),7.72(1H,d,J=7Hz),8.29 (1H,d,J=7Hz),8.37(1H,s) Mass spectrum m/z:358(M^+)

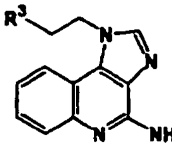
Example 88

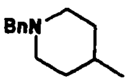
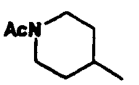
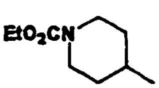
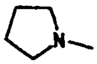
tert-Butyl 4-[2-(4-amino-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]-1-piperidinecarboxylate

[0102] A mixture of 4.40 g of tert-butyl 4-[2-(4-phenoxy-1H-imidazo[4,5-c]-quinolin-1-yl)ethyl]-1-piperidinecarboxylate and 34 5 g of ammonium acetate was stirred at 140°C for 3 hours. The reaction mixture was added with water, adjusted to pH 9 with 10% aqueous sodium hydroxide solution, and extracted with methylene chloride. The extract was washed with sarurated brine, and dried, and then the solvent was evaporated. The resulting residue was purified by alumina column chromatography using methylene chloride - methanol (100:1 to 20:1) as eluting solvents, and washed with diisopropyl ether to give 1.88 g of colorless crystals. Recrystallization from ethyl acetate gave colorless crystals having the melting point of from 193 to 193.5°C.

Elemental analysis for $C_{22}H_{29}N_5O_2$			
Calculated % Found %	C, 66.81; C, 66.93;	H, 7.39; H, 7.46;	N, 17.71 N, 17.66

[0103] In accordance with the method of Example 88, the compounds of Examples 89 through 92 were obtained.



Example	R^3	Physical properties (Recrystallization solvent)
89		colorless crystals (EtOH) mp,191.5-192℃ Elemental analysis for $C_{24}H_{27}N_5$ Calcd.%: C, 74.77; H, 7.06; N, 18.17 Found%: C, 74.87; H, 7.18; N, 18.06
90		colorless crystals (MeOH) mp,231.5-232.5℃ Elemental analysis for $C_{19}H_{23}N_5O$ Calcd.%: C, 67.63; H, 6.87; N, 20.76 Found%: C, 67.46; H, 6.79; N, 20.63
91		colorless crystals (EtOH) mp,166-167℃ Elemental analysis for $C_{20}H_{25}N_5O_2$ Calcd.%: C, 65.37; H, 6.86; N, 19.06 Found%: C, 65.52; H, 6.76; N, 18.83
92		pale yellow crystals [fumarate] (DMF-iso-Pr_2O) mp,195-197℃ (decomposition) Elemental analysis for $C_{18}H_{19}N_5 \cdot C_4H_4O_4 \cdot 5/4H_2O$ Calcd.%: C, 57.20; H, 6.12; N, 16.68 Found%: C, 57.20; H, 6.23; N, 16.53

Example 93

tert-Butyl 4-[2-(4-dimethylamino-2-phenyl-1H-imidazo[4,5-c]quinolin-1-yl)-ethyl]-1-piperidinecarboxylate

[0104] A mixture of 0.69 g of tert-butyl 4-[2-(4-chloro-2-phenyl-1H-imidazo[4,5-c]-quinolin-1-yl)ethyl]-1-piperidinecarboxylate and 7 ml of 50% aqueous dimethylamine solution was stirred in a sealed tube at 80°C of outer temperature for 2 hours. The reaction solution was added with water and extracted with ethyl acetate. The extract was washed successively with water and saturated brine, and dried, and the solvent was evaporated. The residue was washed successively with isopropanol and diisopropyl ether to give 0.52 g of colorless crystals. Recrystallization from isopropanol gave colorless crystals having the melting point of from 170.5 to 171.5°C.

Elemental analysis for $C_{30}H_{37}N_5O_2$			
Calculated %	C, 72.12;	H, 7.46;	N, 14.02
Found %	C, 71.95;	H, 7.72;	N, 13.83

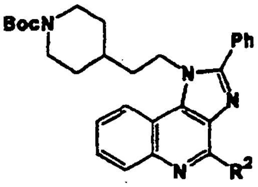
Example 94

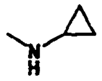
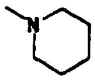
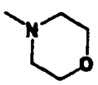
tert-Butyl 4-[2-[4-(4-methylpiperazin-1-yl)-2-phenyl-1H-imidazo[4,5-c]-quinolin-1-yl]ethyl]-1-piperidinecarboxylate

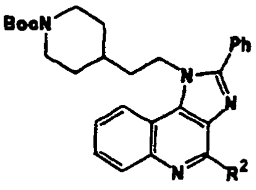
[0105] A mixture of 0.80 g of tert-butyl 4-[2-(4-chloro-2-phenyl-1H-imidazo-[4,5-c]quinolin-1-yl)ethyl]-1-piperidinecarboxylate and 1 ml of N-methylpiperazine was stirred at 80°C for 6 hours. The reaction mixture was added with saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was dried, and the solvent was evaporated. The residue was purified by alumina column chromatography using ethyl acetate - n-heptane (1:3 to 1:1) as eluting solvents, and washed with a mixture of diisopropyl ether and n-heptane to give 0.74 g of colorless crystals. Recrystallization from ethyl acetate gave colorless needles having the melting point of from 140 to 141°C

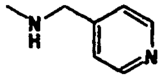
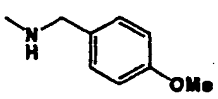
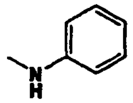
Elemental analysis for $C_{33}H_{42}N_8O_2$			
Calculated %	C, 71.45;	H, 7.63;	N, 15.15
Found %	C, 71 23;	H, 7.65;	N, 14.99

[0106] In accordance with the methods of Examples 93 and 94, the compounds of Examples 95 through 102 were obtained.



Example	R²	Physical properties (Recrystallization solvent)
95	NHMe	colorless crystals (iso-PrOH) mp,161-162℃ Elemental analysis for $C_{29}H_{35}N_5O_2 \cdot 1/2H_2O$ Calcd.%: C, 70.42; H, 7.34; N, 14.16 Found%: C, 70.31; H, 7.23; N, 13.95
96		colorless crystals (iso-Pr_2O) mp,162-162.5℃ Elemental analysis for $C_{31}H_{37}N_5O_2 \cdot 1/2H_2O$ Calcd.%: C, 71.51; H, 7.38; N, 13.45 Found%: C, 71.73; H, 7.35; N, 13.09
97		colorless needles (MeOH) mp,171-172℃ Elemental analysis for $C_{33}H_{41}N_5O_2$ Calcd.%: C, 73.44; H, 7.66; N, 12.98 Found%: C, 73.44; H, 7.88; N, 12.93
98		colorless crystals (iso-PrOH) mp,189-190℃ Elemental analysis for $C_{32}H_{39}N_5O_3$ Calcd.%: C, 70.95; H, 7.26; N, 12.93 Found%: C, 71.22; H, 7.47; N, 12.94
99	NHBn	pale brown amorphous solid NMR spectrum δ ($CDCl_3$)ppm: 0.99-1.06(2H,m),1.25-1.40(3H,m),1.43(9H,s),1.80-1.90(2H,m),2.50-2.60(2H,m),3.95-4.05(2H,m),4.59(2H,t,J=7.5Hz),4.98(2H,d,J=5.5Hz),6.11(1H,t,J=5.5Hz),7.24-7.28(1H,m),7.30-7.35(3H,m),7.48(2H,d,J=7.5Hz),7.50-7.55(4H,m),7.60-7.65(2H,m),7.94-7.96(2H,m) IR spectrum ν (KBr) cm^{-1}:3436,1690 Mass spectrum m/z:561(M^+)



Example	R^2	Physical properties
100		pale yellow amorphous solid NMR spectrum δ ($CDCl_3$)ppm: 1.00-1.08(2H,m),1.30-1.35(1H,m),1.38-1.42(2H,m),1.43(9H,s),1.83-1.90(2H,m),2.57(2H,brs),3.98(2H,brs),4.61(2H,t,J=7.5Hz),4.99(2H,d,J=6Hz),7.33-7.35(1H,m),7.39(2H,d,J=6Hz),7.51-7.59(4H,m),7.64-7.67(2H,m),7.88-7.89(1H,m),7.96-7.97(1H,m),8.53(2H,d,J=6Hz) IR spectrum ν (KBr) cm^{-1}:3428,1692 Mass spectrum m/z:562(M^+)
101		pale brown amorphous solid NMR spectrum δ ($CDCl_3$)ppm: 0.98-1.06(2H,m),1.25-1.40(3H,m),1.43(9H,s),1.80-1.85(2H,m),2.50-2.60(2H,m),3.79(3H,s),3.90-4.00(2H,m),4.59(2H,t,J=7.5Hz),4.87(2H,d,J=5.5Hz),6.05(1H,brs),6.86(2H,d,J=8.5Hz),7.31(1H,t,J=7.5Hz),7.40(2H,d,J=8.5Hz),7.51-7.60(4H,m),7.60-7.65(2H,m),7.94(2H,d,J=8.5Hz) IR spectrum ν (KBr) cm^{-1}:3432,1692 Mass spectrum m/z:591(M^+)
102		colorless amorphous solid NMR spectrum δ (DMSO-d_6)ppm: 0.87(2H,q,J=5Hz),1.20-1.35(3H,m),1.36(9H,s),1.75(2H,q,J=7.5Hz),2.54(2H,t,J=12.5Hz),3.77(2H,d,J=12.5Hz),4.64(2H,t,J=7.5Hz),6.99(1H,t,J=8Hz),7.34(2H,t,J=8Hz),7.44(1H,t,J=7.5Hz),7.56(1H,t,J=7.5Hz),7.60-7.67(3H,m),7.76-7.82(2H,m),7.87(1H,d,J=7.5Hz),8.16(1H,d,J=7.5Hz),8.24(2H,d,J=8Hz),9.03(1H,s) IR spectrum ν (KBr) cm^{-1}:2932,1692 Mass spectrum m/z:547(M^+)

Example 103

4-Amino-2-phenyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline trifluoroacetate

[0107] A mixture of 0.30 g of tert-butyl 4-[2-[4-(4-methoxybenzylamino)-2-phenyl-1H-imidazo[4,5-c]quinolin-1-yl] ethyl]-1-piperidinecarboxylate and 9 ml of trifluoroacetic acid was stirred at 65°C of outer temperature for 6 hours. The reaction solution was concentrated, and the residue was added with isopropanol. The precipitated crystals were collected by filtration, and washed with diisopropyl ether to give 0.31 g of pale yellow crystals. Recrystallization from a mixture of ethanol and isopropanol gave colorless crystals having the melting point of from 223 to 224°C.

Elemental analysis for $C_{23}H_{25}N_5 \cdot 2CF_3CO_2H \cdot H_2O$			
Calculated %	C, 52.51;	H, 4.73;	N, 11.34
Found %	C, 52.61;	H, 4.45;	N, 11.61

Example 104

1-[2-(4-Chloro-2-phenyl-1H-imidazo [4,5-c]quinolin-1-yl)ethyl]-4-piperidinone

[0108] A mixture of 0.39 g of 1-[2-(4-chloro-2-phenyl-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]-4,4-ethylenedioxypiperidine and 4 ml of concentrated sulfuric acid was stirred at room temperature for 30 minutes. The reaction mixture was poured into ice-water, adjusted to pH 11 with 10% aqueous sodium hydroxide solution, and extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogencarbonate solution and dried, and then the solvent was evaporated to give 0.42 g of a colorless liquid. The resulting liquid was purified by alumina column chromatography using ethyl acetate - n-heptane (1:1) as an eluting solvent to give 0.32 g of colorless crystals Recrystallization from isopropanol gave colorless needles having the melting point of from 163 to 165°C.

Elemental analysis for $C_{23}H_{21}ClN_4O$			
Calculated %	C, 68.23;	H, 5.23;	N, 13.84
Found %	C, 68 26;	H, 5.31;	N, 13.78

Example 105

1-[2-(4-Chloro-2-phenyl-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]-4-piperidinone oxime

[0109] A mixture of 0.20 g of 1-[2-(4-chloro-2-phenyl-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]-4-piperidinone, 0.04 g of hydroxylamine hydrochloride, 0.09 g of sodium acetate and 4 ml of methanol was stirred at room temperature for 1 hour. The reaction solution was concentrated, and the residue was added with aqueous sodium hydrogencarbonate solution, and extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogencarbonate solution, and dried, and the solvent was evaporated to give 0.25 g of a colorless solid. Recrystallization from ethyl acetate gave colorless crystals having the melting point of from 201 to 207°C (decomposition).

Elemental analysis for $C_{23}H_{22}ClN_5O \cdot 1/2H_2O$			
Calculated %	C, 64.41;	H, 5.40;	N, 16.33
Found %	C, 64.75;	H, 5.32;	N, 16.09

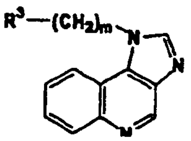
Example 106

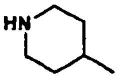
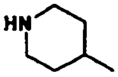
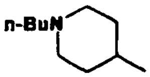
tert-Butyl 4-[2-(2-phenyl-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]-1-piperidinecarboxylate

[0110] A suspension of 0.80 g of tert-butyl 4-[2-(4-chloro-2-phenyl-1H-imidazo-[4,5-c]quinolin-1-yl)ethyl]-1-piperidinecarboxylate and 0.30 g of 5% palladium on carbon in 80 ml of methanol was catalytically hydrogenated at ordinary temperature under atmospheric pressure for 12 hours. After the reaction, the catalyst was filtered off, and the filtrate was concentrated. The residue was purified by silica gel column chromatography using ethyl acetate - n-heptane (1: 1 to 4:1) as eluting solvents and washed with diisopropyl ether to give 0.49 g of pale yellow crystals. Recrystallization from diisopropyl ether gave colorless crystals having the melting point of from 138 to 139°C.

Elemental analysis for $C_{28}H_{32}N_4O_2$			
Calculated %	C, 73.66;	H, 7.06;	N, 12.27
Found %	C, 73.46;	H, 7.21;	N, 12.17

[0111] In accordance with the method of Example 106, the compounds of Examples 107 through 109 were obtained.



Example	R^3	m	Physical properties (Recrystallization solvent)
107		1	colorless crystals [hydrochloride] (MeOH) mp,258-261℃ (decomposition) Elemental analysis for $C_{16}H_{18}N_4 \cdot 2HCl \cdot H_2O$ Calcd.%: C, 53.79; H, 6.21; N, 15.68 Found%: C, 53.49; H, 6.14; N, 15.67
108		2	colorless crystals [hydrochloride] (MeOH-$ClCH_2CH_2Cl$) mp,220-233℃ (decomposition) Elemental analysis for $C_{17}H_{20}N_4 \cdot 2HCl \cdot 1/2H_2O$ Calcd.%: C, 56.36; H, 6.40; N, 15.46 Found%: C, 56.36; H, 6.18; N, 15.35
109		2	colorless crystals [hydrochloride] (MeOH-iso-Pr_2O) mp,225-238℃ (decomposition) Elemental analysis for $C_{21}H_{28}N_4 \cdot 2HCl \cdot 1/8H_2O$ Calcd.%: C, 61.27; H, 7.41; N, 13.61 Found%: C, 61.03; H, 7.44; N, 13.50

Example 110

4-Chloro-2-phenyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline hydrochloride and fumarate

[0112] A mixture of 3.64 g of 4-chloro-2-phenyl-1-[2-(N-triphenylmethyl-4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline, 30 ml of methanol and 10 ml of trifluoroacetic acid was stirred at room temperature for 1 hour. The reaction mixture was concentrated, and the residue was washed successively with ethyl acetate and diethyl ether to give pale brown crystals (trifluoroacetate). The resulting crystals were added with ethyl acetate, and extracted with water. The aqueous layer was adjusted to pH 11 with 10% aqueous sodium hydroxide solution, and extracted with a mixture of 1,2-dichloroethane and methanol. The extract was washed with saturated brine, and dried, and then the solvent was evaporated to give 1.74 g of a colorless liquid. A part of the colorless liquid was converted into hydrochloride in a conventional method. Recrystallization from methanol gave colorless crystals having the melting point of from 257 to 265°C (decomposition). In the same manner, fumarate was prepared in a conventional method. Recrystallization from methanol gave colorless crystals having the melting point of from 185.5 to 186.5°C (decomposition).

Hydrochloride:

[0113]

Elemental analysis for $C_{23}H_{23}ClN_4 \cdot HCl \cdot H_2O$			
Calculated %	C, 62.02;	H, 5.88;	N, 12.58
Found %	C, 62.08;	H, 5.77;	N, 12.60

Fumarate:

[0114]

Elemental analysis for $C_{23}H_{23}ClN_4 \cdot C_4H_4O_4 \cdot H_2O$			
Calculated % Found %	C, 61.77; C, 62.04;	H, 5.57; H, 5.40;	N, 10.67 N, 10.70

Example 111

4-Phenoxy-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline trifluoroacetate

[0115] To a solution of 0.30 g of tert-butyl 4-[2-(4-phenoxy-1H-imidazo[4,5-c]-quinolin-1-yl)ethyl]-1-piperidinecarboxylate in 10 ml of methylene chloride, 1 ml of trifluoroacetic acid was added at room temperature, and the mixture was stirred for 1.5 hours. The reaction solution was concentrated. The resulting pale yellow solid was washed successively with isopropanol and diisopropyl ether to give 0.36 g of colorless crystals. Recrystallization from a mixture of methylene chloride and ethanol gave colorless crystals having the melting point of from 211 to 216°C.

Elemental analysis for $C_{23}H_{24}N_4O \cdot CF_3CO_2H \cdot 1/8H_2O$			
Calculated % Found %	C, 61.44; C, 61.26;	H, 5.21; H, 5.05;	N, 11.46 N, 11.47

Example 112

4-Chloro-2-phenyl-1-[2-(1-piperazinyl)ethyl]-1H-imidazo[4,5-c]quinoline methanesulfonate

[0116] To a solution of 1 20 g of tert-butyl 4-[2-(4-chloro-2-phenyl-1H-imidazo-[4,5-c]quinolin-1-yl)ethyl]-1-piperazinecarboxylate in 12 ml of 1,2-dichloroethane, 1.2 ml of methanesulfonic acid was added, and the mixture was stirred at room temperature for 5 minutes. The reaction mixture was added with isopropanol and ethanol, and the precipitated crystals were collected by filtration to give 1.24 g of colorless crystals. Recrystallization from methanol gave colorless crystals having the melting point of from 256 to 270°C (decomposition).

Elemental analysis for $C_{22}H_{22}ClN_5 \cdot 2CH_3SO_3H$			
Calculated % Found %	C, 49.35; C, 49.60;	H, 5.18; H, 5.11;	N, 11.99 N, 12.16

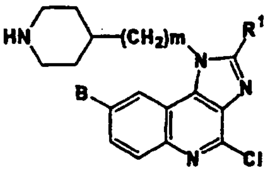
Example 113

4-Amino-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline hydrochloride

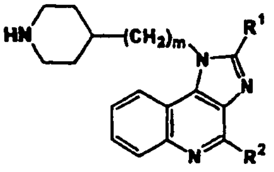
[0117] A mixture of 1.57 g of tert-butyl 4-[2-(4-amino-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]-1-piperidinecarboxylate and 40 ml of ethyl acetate solution of hydrogen chloride was stirred at room temperature for 5 hours. The reaction mixture was added with water, adjusted to pH 10 with 10% aqueous sodium hydroxide solution, and extracted with methylene chloride. The extract was dried, and the solvent was evaporated. The resulting residue was washed with ethyl acetate to give 1.01 g of pale brown crystals. The resulting crystals were purified by alumina column chromatography using methylene chloride - methanol (40:1 to 20:1) as eluting solvents, and washed with diisopropyl ether to give colorless crystals. Hydrochloride was prepared in a conventional method. Recrystallization from ethanol gave colorless crystals having the melting point of from 243 to 244°C (decomposition).

Elemental analysis for $C_{17}H_{21}N_5 \cdot HCl \cdot 3/4H_2O$			
Calculated % Found %	C, 59.12; C, 59.10;	H, 6.86; H, 6.83;	N, 20.28 N, 20.30

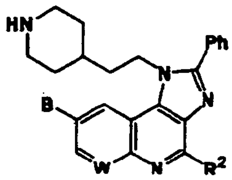
[0118] In accordance with the methods of Examples 110 through 113, the compounds of Examples 114 through 186 were obtained.



Example	R^1	B	m	Physical properties (Recrystallization solvent)
114	Ph	H	0	colorless crystals ($ClCH_2CH_2Cl$-AcOEt) mp,253-256°C (decomposition) Elemental analysis for $C_{21}H_{19}ClN_4$ Calcd.%: C, 69.51; H, 5.28; N, 15.44 Found%: C, 69.29; H, 5.19; N, 15.27
115	H	H	1	colorless crystals [hydrochloride] (MeOH-EtOH) mp,273-286°C (decomposition) Elemental analysis for $C_{16}H_{17}ClN_4$-2HCl Calcd.%: C, 51.42; H, 5.12; N, 14.99 Found%: C, 51.47; H, 5.08; N, 14.85
116	Ph	H	1	colorless crystals [fumarate](MeOH) mp,268-271.5°C (decomposition) Elemental analysis for $C_{22}H_{21}ClN_4$-$1/2C_4H_4O_4$-$3/2H_2O$ Calcd.%: C, 62.40; H, 5.67; N, 12.13 Found%: C, 62.52; H, 5.28; N, 12.15
117	H	H	2	colorless crystals [hydrochloride] (EtOH) mp,258-267°C (decomposition) Elemental analysis for $C_{17}H_{19}ClN_4$-HCl Calcd.%: C, 58.13; H, 5.74; N, 15.95 Found%: C, 57.88; H, 5.46; N, 15.78
118	H	Cl	2	colorless crystals [trifluoroacetate] (MeOH-iso-Pr_2O) mp,204-207.5°C Elemental analysis for $C_{17}H_{18}Cl_2N_4$-CF_3CO_2H-$1/4H_2O$ Calcd.%: C, 48.78; H, 4.20; N, 11.98 Found%: C, 48.76; H, 4.34; N, 11.89



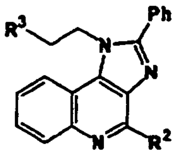
Example	R^1	R^2	m	Physical properties (Recrystallization solvent)
119	OH	Cl	2	pale brown crystals ($ClCH_2CH_2Cl$-MeOH) mp,240-245°C (decomposition) Elemental analysis for $C_{17}H_{19}ClN_4O$-1/2H_2O Calcd.%: C, 60 09; H, 5.93; N, 16.49 Found%: C, 60.32; H, 5.72; N, 16.41
120	Me	Cl	2	pale brown crystals [trifluoroacetate] (EtOH) mp,201-202°C Elemental analysis for $C_{18}H_{21}ClN_4$-CF_3CO_2H-5/4H_2O Calcd.%: C, 51.62; H, 5.31; N, 12.04 Found%: C, 51.82; H, 5.12; N, 12 22
121	CF_3	Cl	2	colorless crystals [trifluoroacetate] (EtOH) mp,233-235°C Elemental analysis for $C_{18}H_{18}ClF_3N_4$-CF_3CO_2H Calcd.%: C, 48.35; H, 3.85; N, 11.28 Found%: C, 48.31; H, 3.88; N, 11.21
122	Ph	H	2	colorless crystals [hydrochloride](EtOH) mp,191.5-192.5°C Elemental analysis for $C_{23}H_{24}N_4$-2HCl-H_2O Calcd.%: C, 61.74; H, 6.31; N, 12.52 Found%: C, 61.69; H, 6.51; N, 12.44
123	Ph	Cl	3	colorless fine needles[trifluoroacetate] (EtOH) mp,260-263°C (decomposition) Elemental analysis for $C_{24}H_{25}ClN_4 \cdot CF_3CO_2H$ Calcd.%: C, 60.17; H, 5.05; N, 10.80 Found%: C, 59.94; H, 5.08; N, 10.80

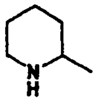
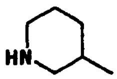
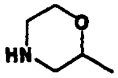
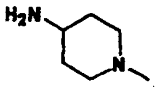
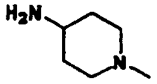


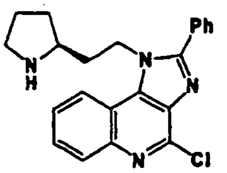
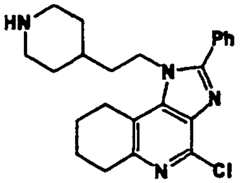
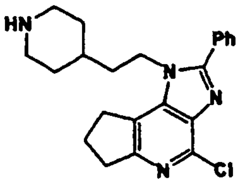
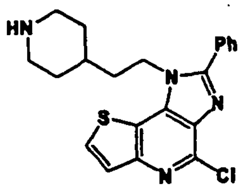
Example	R^2	B	W	Physical properties (Recrystallization solvent)
124	Me	H	CH	colorless crystals [hydrochloride](EtOH) mp,199-201 °C Elemental analysis for $C_{24}H_{28}N_4$-HCl-7/2H_2O Calcd.%: C, 61.33; H, 7.29; N, 11.92 Found%: C, 61.21; H, 7.26; N, 11.80

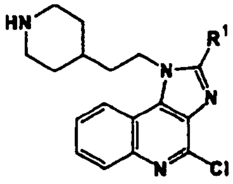
(continued)

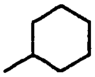
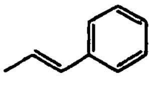
Example	R^2	B	W	Physical properties (Recrystallization solvent)
125	Cl	Cl	CH	colorless crystals [trifluoroacetate](MeOH) mp,249-255°C (decomposition) Elemental analysis for $C_{23}H_{22}Cl_2N_4$-CF_3CO_2H Calcd.%: C, 55.67; H, 4.30; N, 10.39 Found%: C, 55.75; H, 4.00; N, 10.47
126	Cl	Me	CH	colorless fine needles[trifluoroacetate] (MeOH) mp,255-262°C (decomposition) Elemental analysis for $C_{24}H_{25}ClN_4$- CF_3CO_2H Calcd.%: C, 60.17; H, 5.05; N, 10.80 Found%: C, 59.95; H, 5 03; N, 10.79
127	Cl	MeO	CH	pale yellow crystals (EtOH) mp,169-170°C Elemental analysis for $C_{24}H_{25}ClN_4O$-$1/2H_2O$ Calcd.%: C, 67.05; H, 6.10; N, 13.03 Found%: C, 67.32; H, 6.06; N, 13.02
128	Cl	H	N	colorless crystals [trifluoroacetate](MeOH) mp,260-268°C (decomposition) Elemental analysis for $C_{22}H_{22}ClN_5$-CF_3CO_2H Calcd.%: C, 56.98; H, 4.58; N, 13.84 Found%: C, 56.76; H, 4 47; N, 13.82

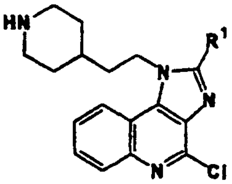


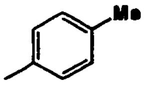
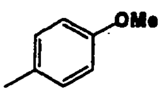
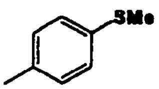
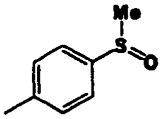
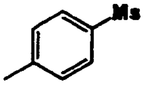
Example	R²	R³	Physical properties (Recrystallization solvent)
129	Cl		colorless prisms (MeOH) mp,191-193℃ Elemental analysis for $C_{23}H_{23}ClN_4$ Calcd.%: C, 70.67; H, 5.93; N, 14.33 Found%: C, 70.70; H, 6.08; N, 14.28
130	Cl		colorless crystals (AcOEt) mp,156.5-157.5℃ Elemental analysis for $C_{23}H_{23}ClN_4$ Calcd.%: C, 70.67; H, 5.93; N, 14.33 Found%: C, 70.64; H, 5.92; N, 14.21
131	Cl		colorless crystals (EtOH) mp,169-171℃ Elemental analysis for $C_{22}H_{21}ClN_4O$ Calcd.%: C, 67.26; H, 5.39; N, 14.26 Found%: C, 67.31; H, 5.55; N, 14.32
132	Cl		colorless crystals [trifluoroacetate] (iso-PrOH) mp,158-163℃ (decomposition) Elemental analysis for $C_{23}H_{24}ClN_5 \cdot 2CF_3CO_2H \cdot 3/2H_2O$ Calcd.%: C, 49.06; H, 4.42; N, 10.60 Found%: C, 49.04; H, 4.41; N, 10.73
133	Me		pale brown crystals (AcOEt) mp,88-89℃ Elemental analysis for $C_{24}H_{27}N_5 \cdot H_2O$ Calcd.%: C, 71.44; H, 7.24; N, 17.36 Found%: C, 71.25; H, 7.23; N, 17.03

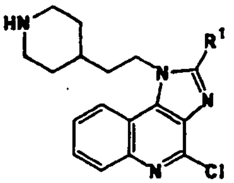
Example		Physical properties (Recrystallization solvent)
134		colorless fine needles[fumarate](EtOH) mp,261-272℃ (decomposition) Elemental analysis for $C_{22}H_{21}ClN_4 \cdot 1/2C_4H_4O_4 \cdot 5/2H_2O$ Calcd.%: C, 60.06; H, 5.88; N, 11.67 Found%: C, 60.07; H, 5.89; N, 11.60 Specific rotation $[\alpha]_D^{20}$: -12.0° (c=0.1, DMSO)
135		colorless crystals [trifluoroacetate] (EtOH) mp,215-221℃ (decomposition) Elemental analysis for $C_{23}H_{27}ClN_4 \cdot CF_3CO_2H$ Calcd.%: C, 59.00; H, 5.55; N, 11.01 Found%: C, 58.85; H, 5.63; N, 11.05
136		pale brown crystals [trifluoroacetate] (MeOH-iso-PrOH) mp,225-232℃ (decomposition) Elemental analysis for $C_{22}H_{25}ClN_4 \cdot CF_3CO_2H$ Calcd.%: C, 58.24; H, 5.29; N, 11.32 Found%: C, 58.09; H, 5.29; N, 11.32
137		pale brown crystals [trifluoroacetate] (EtOH) mp,224-224.5℃ Elemental analysis for $C_{21}H_{21}ClN_4S \cdot CF_3CO_2H \cdot 3/2H_2O$ Calcd.%: C, 51.35; H, 4.68; N, 10.41 Found%: C, 51.65; H, 4.32; N, 10.16

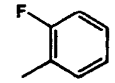
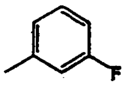
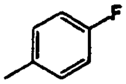
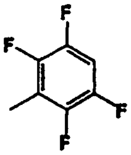
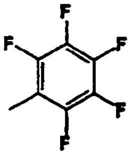


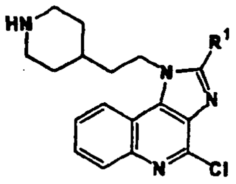
Example	R^1	Physical properties (Recrystallization solvent)
138	n-Bu	colorless crystals (AcOEt) mp,130-131℃ Elemental analysis for $C_{21}H_{27}ClN_4$ Calcd.%: C, 68.00; H, 7.34; N, 15.10 Found%: C, 67.76; H, 7.59; N, 14.96
139		colorless crystals [trifluoroacetate](EtOH) mp,139-139.5℃ Elemental analysis for $C_{23}H_{29}ClN_4\cdot3/2CF_3CO_2H\cdot H_2O$ Calcd.%: C, 53.29; H, 5.59; N, 9.56 Found%: C, 53.23; H, 5.33; N, 9.56
140	Bn	pale brown crystals (AcOEt-iso-Pr_2O) mp,230-234℃(decomposition) Elemental analysis for $C_{24}H_{25}ClN_4\cdot1/4H_2O$ Calcd.%: C, 70.40; H, 6.28; N, 13.68 Found%: C, 70.41; H, 6.27; N, 13.54
141		pale yellow crystals [methanesulfonate] (MeOH) mp,196-207℃(decomposition) Elemental analysis for $C_{25}H_{25}ClN_4\cdot2CH_3SO_3H\cdot H_2O$ Calcd.%: C, 51.71; H, 5.62; N, 8.93 Found%: C, 51.59; H, 5.42; N, 8.87

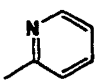
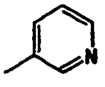
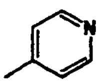
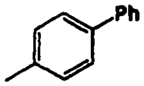
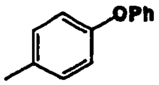


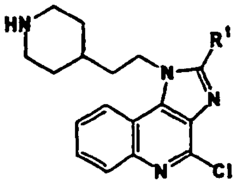
Example	R^1	Physical properties (Recrystallization solvent)
142		colorless crystals [fumarate](MeOH) mp,224-229℃ (decomposition) Elemental analysis for $C_{24}H_{23}ClN_4 \cdot C_4H_4O_4 \cdot H_2O$ Calcd.%: C, 62.39; H, 5.80; N, 10.39 Found%: C, 62.46; H, 5.51; N, 10.42
143		colorless crystals [fumarate](EtOH) mp,213.5-216℃ (decomposition) Elemental analysis for $C_{24}H_{23}ClN_4O \cdot C_4H_4O_4 \cdot 1/4H_2O$ Calcd.%: C, 62.10; H, 5.49; N, 10.35 Found%: C, 61.94; H, 5.45; N, 10.30
144		colorless crystals [trifluoroacetate] (MeOH-iso-Pr_2O) mp,253-257℃ (decomposition) Elemental analysis for $C_{24}H_{23}ClN_4S \cdot CF_3CO_2H \cdot 1/2H_2O$ Calcd.%: C, 55.76; H, 4.86; N, 10.00 Found%: C, 55.67; H, 4.59; N, 9.99
145		colorless crystals [trifluoroacetate](EtOH) mp,218-225℃ (decomposition) Elemental analysis for $C_{24}H_{23}ClN_4OS \cdot CF_3CO_2H$ Calcd.%: C, 55.07; H, 4.62; N, 9.88 Found%: C, 54.91; H, 4.69; N, 9.77
146		colorless crystals [trifluoroacetate](MeOH) mp,270-277℃ (decomposition) Elemental analysis for $C_{24}H_{23}ClN_4O_2S \cdot CF_3CO_2H$ Calcd.%: C, 53.56; H, 4.49; N, 9.61 Found%: C, 53.51; H, 4.50; N, 9.62

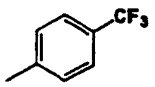
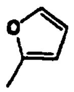
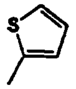
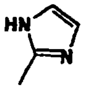
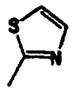


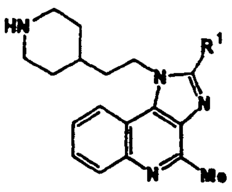
Example	R¹	Physical properties (Recrystallization solvent)
147		colorless crystals [fumarate](EtOH) mp,192-198℃ (decomposition) Elemental analysis for $C_{23}H_{22}ClFN_4 \cdot C_4H_4O_4 \cdot H_2O$ Calcd.%: C, 59.72; H, 5.20; N, 10.32 Found%: C, 59.81; H, 5.07; N, 10.33
148		colorless crystals [fumarate](MeOH-iso-PrOH) mp,184-187℃ (decomposition) Elemental analysis for $C_{23}H_{22}ClFN_4 \cdot C_4H_4O_4 \cdot H_2O$ Calcd.%: C, 59.72; H, 5.20; N, 10.32 Found%: C, 60.00; H, 4.91; N, 10.34
149		colorless crystals [fumarate](MeOH) mp,204-209℃ (decomposition) Elemental analysis for $C_{23}H_{22}ClFN_4 \cdot C_4H_4O_4 \cdot H_2O$ Calcd.%: C, 59.72; H, 5.20; N, 10.32 Found%: C, 59.53; H, 4.92; N, 10.41
150		colorless crystals [trifluoroacetate](EtOH) mp,260-263℃ (decomposition) Elemental analysis for $C_{23}H_{19}ClF_4N_4 \cdot CF_3CO_2H \cdot H_2O$ Calcd.%: C, 50.47; H, 3.73; N, 9.42 Found%: C, 50.33; H, 3.53; N, 9.51
151		colorless crystals [trifluoroacetate](MeOH) mp,259-261℃ (decomposition) Elemental analysis for $C_{23}H_{18}ClF_5N_4 \cdot CF_3CO_2H$ Calcd.%: C, 50.48; H, 3.22; N, 9.42 Found%: C, 50.28; H, 3.28; N, 9.46

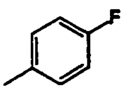
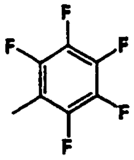
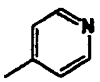
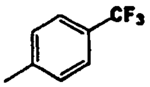
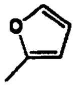


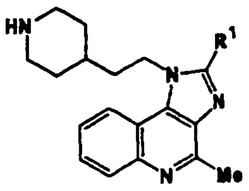
Exampl	R^1	Physical properties (Recrystallization solvent)
152		colorless crystals [methanesulfonate] (EtOH) mp,195-202℃ (decomposition) Elemental analysis for $C_{22}H_{22}ClN_5 \cdot CH_3SO_3H \cdot 5/4H_2O$ Calcd.%: C, 54.11; H, 5.63; N, 13.72 Found%: C, 54.13; H, 5.45; N, 13.63
153		colorless crystals [fumarate](MeOH-EtOH) mp,181-185.5℃ (decomposition) Elemental analysis for $C_{22}H_{22}ClN_5 \cdot C_4H_4O_4 \cdot H_2O$ Calcd.%: C, 59.37; H, 5.37; N, 13.31 Found%: C, 59.37; H, 5.11; N, 13.37
154		pale yellow fine needles [trifluoroacetate] (EtOH) mp,197.5-204℃ (decomposition) Elemental analysis for $C_{22}H_{22}ClN_5 \cdot CF_3CO_2H \cdot 1/4H_2O$ Calcd.%: C, 56.47; H, 4.64; N, 13.72 Found%: C, 56.45; H, 4.58; N, 13.72
155		colorless crystals [trifluoroacetate](EtOH) mp,250-255℃ (decomposition) Elemental analysis for $C_{29}H_{27}ClN_4 \cdot CF_3CO_2H$ Calcd.%: C, 64.08; H, 4.86; N, 9.64 Found%: C, 63.81; H, 4.92; N, 9.63
156		colorless crystals [trifluoroacetate](EtOH) mp,144.5-145.5℃ Elemental analysis for $C_{29}H_{27}ClN_4O \cdot CF_3CO_2H \cdot 3/2H_2O$ Calcd.%: C, 59.66; H, 5.01; N, 8.98 Found%: C, 59.44; H, 4.71; N, 9.04

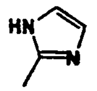
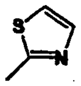
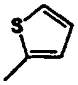
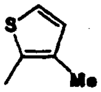
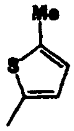


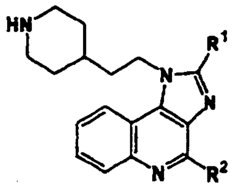
Example	R^1	Physical properties (Recrystallization s lvent)
157		pale green crystals[trifluoroacetate](EtOH) mp.174-175℃ Elemental analysis for $C_{24}H_{22}ClF_3N_4 \cdot CF_3CO_2H \cdot 5/4H_2O$ Calcd.%: C, 52.44; H, 4.32; N, 9.41 Found%: C, 52.54; H, 4.19; N, 9.53
158		colorless crystals [trifluoroacetate](MeOH) mp,231-241℃(decomposition) Elemental analysis for $C_{21}H_{21}ClN_4O \cdot CF_3CO_2H \cdot 1/2H_2O$ Calcd.%: C, 54.82; H, 4.60; N, 11.12 Found%: C, 54.73; H, 4.42; N, 11.21
159		colorless crystals [trifluoroacetate](EtOH) mp,258-261℃(decomposition) Elemental analysis for $C_{21}H_{21}ClN_4S \cdot CF_3CO_2H \cdot 1/4H_2O$ Calcd.%: C, 53.59; H, 4.40; N, 10.87 Found%: C, 53.53; H, 4.33; N, 10.90
160		colorless crystals [trifluoroacetate](MeOH) mp,270-273℃(decomposition) Elemental analysis for $C_{20}H_{21}ClN_6 \cdot CF_3CO_2H \cdot 1/2H_2O$ Calcd.%: C, 52.44; H, 4.60; N, 16.68 Found%: C, 52.15; H, 4.74; N, 16.95
161		pale brown crystals [trifluoroacetate] (EtOH-Et_2O) mp,203-203.5℃ Elemental analysis for $C_{20}H_{20}ClN_5S \cdot CF_3CO_2H$ Calcd.%: C, 51.61; H, 4.13; N, 13.68 Found%: C, 51.48; H, 4.22; N, 13.52

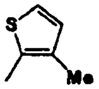
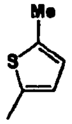
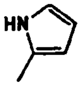
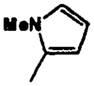
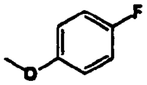


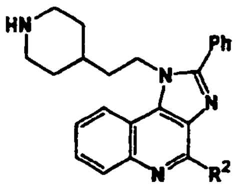
Example	R¹	Physical properties (Recrystallization solvent)
162		pale yellow crystals [hydrochloride](iso-PrOH) mp,245-249℃ (decomposition) Elemental analysis for $C_{24}H_{25}FN_4 \cdot 2HCl \cdot 3/4H_2O$ Calcd.%: C, 60.70; H, 6.05; N, 11.80 Found%: C, 60.81; H, 5.93; N, 11.72
163		colorless crystals [hydrochloride](EtOH) NMR spectrum δ (DMSO-d_6)ppm:1.30-1.40(2H,m),1.55-1.70(1H,m),1.70-1.80(4H,m),2.65-2.80(2H,m),3.10-3.25(2H,m),3.17(3H,s),4.73(2H,t,J=7.5Hz),7.97(1H,t,J=7.5Hz),8.04(1H,t,J=7.5Hz),8.55-8.65(2H,m),8.84(1H,brs),9.06(1H,brs)
164		pale brown crystals (AcOEt) mp,176-177.5℃ Elemental analysis for $C_{23}H_{25}N_5$ Calcd.%: C, 74.36; H, 6.78; N, 18.85 Found%: C, 74.09; H, 6.90; N, 18.69
165		colorless crystals [hydrochloride] (MeOH-iso-PrOH) mp,>300℃ Elemental analysis for $C_{25}H_{25}F_3N_4 \cdot 2HCl \cdot 1/2H_2O$ Calcd.%: C, 57.70; H, 5.42; N, 10.77 Found%: C, 57.72; H, 5.12; N, 10.79
166		pale yellow crystals (iso-PrOH) mp,166-167℃ Elemental analysis for $C_{22}H_{24}N_4O \cdot H_2O$ Calcd.%: C, 69.82; H, 6.92; N, 14.80 Found%: C, 69.53; H, 6.97; N, 14.59

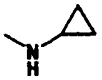


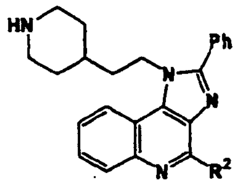
Example	R^1	Physical properties (Recrystallization solvent)
167		colorless crystals [hydrochloride] (EtOH) mp,218-219℃ Elemental analysis for $C_{21}H_{24}N_6 \cdot 3HCl$ Calcd.%: C, 53.68; H, 5.79; N, 17.89 Found%: C, 53.63; H, 6.01; N, 17.89
168		pale yellow crystals [hydrochloride] (MeOH) mp,293-298℃ (decomposition) Elemental analysis for $C_{21}H_{23}N_5S \cdot 2HCl \cdot H_2O$ Calcd.%: C, 53.84; H, 5.81; N, 14.95 Found%: C, 53.59; H, 5.71; N, 14.82
169		pale yellow crystals [hydrochloride] (EtOH) mp,196-199℃ Elemental analysis for $C_{22}H_{24}N_4S \cdot 2HCl \cdot 3H_2O$ Calcd.%: C, 52.48; H, 6.41; N, 11.13 Found%: C, 52.44; H, 6.68; N, 11.13
170		pale yellow crystals [trifluoroacetate] (EtOH) mp,228-229℃ Elemental analysis for $C_{23}H_{26}N_4S \cdot 3/2CF_3CO_2H \cdot 1/2H_2O$ Calcd.%: C, 54.73; H, 5.03; N, 9.82 Found%: C, 54.46; H, 4.91; N, 10.00
171		pale yellow crystals [hydrochloride] (EtOH) mp,274-277℃ (decomposition) Elemental analysis for $C_{23}H_{26}N_4S \cdot 2HCl \cdot 5/4H_2O$ Calcd.%: C, 56.84; H, 6.33; N, 11.53 Found%: C, 56.79; H, 6.11; N, 11.51

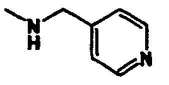
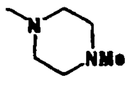
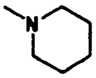
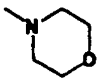


Example	R^1	R^2	Physical properties (Recrystallization solvent)
172		Cl	colorless crystals [trifluoroacetate] (EtOH) mp,189-190℃ Elemental analysis for $C_{22}H_{23}ClN_4S \cdot 3/2CF_3CO_2H$ Calcd.%: C, 51.59; H, 4.24; N, 9.63 Found%: C, 51.54; H, 4.29; N, 9.65
173		Cl	colorless crystals [trifluoroacetate] (EtOH) mp,194-195℃ Elemental analysis for $C_{22}H_{23}ClN_4S \cdot 5/4CF_3CO_2H$ Calcd.%: C, 53.16; H, 4.42; N, 10.12 Found%: C, 53.18; H, 4.39; N, 10.39
174		Me	pale brown crystals [hydrochloride] (EtOH) mp,245.5-246.5℃ Elemental analysis for $C_{22}H_{25}N_5 \cdot 2HCl \cdot 3/2H_2O$ Calcd.%: C, 57.52; H, 6.58; N, 15.24 Found%: C, 57.65; H, 6.33; N, 15.23
175		Me	pale brown crystals [hydrochloride] (EtOH) mp,224-225℃ Elemental analysis for $C_{23}H_{27}N_5 \cdot 2HCl \cdot 5/2H_2O$ Calcd.%: C, 56.21; H, 6.97; N, 14.25 Found%: C, 55.95; H, 6.70; N, 14.23
176	H		colorless prisms[trifluoroacetate] (EtOH-iso-Pr$_2$O) mp,189.5-192.5℃ Elemental analysis for $C_{23}H_{23}FN_4O \cdot CF_3CO_2H$ Calcd.%: C, 59.52; H, 4.80; N, 11.11 Found%: C, 59.41; H, 4.89; N, 11.16



Example	R^2	Physical properties (Recrystallization solvent)
177	OPh	colorless crystals [trifluoroacetate] (EtOH) mp,214.5-215.5℃ Elemental analysis for $C_{29}H_{28}N_4O \cdot CF_3CO_2H \cdot 1/2H_2O$ Calcd.%: C, 65.14; H, 5.29; N, 9.80 Found%: C, 65.40; H, 5.07; N, 9.85
178	NHPh	colorless crystals (MeOH-iso-PrOH) mp,191-194℃ Elemental analysis for $C_{29}H_{29}N_5$ Calcd.%: C, 77.82; H, 6.53; N, 15.65 Found%: C, 77.76; H, 6.59; N, 15.56
179	NHMe	pale yellow crystals [hydrochloride] (iso-PrOH) mp,209-210℃ Elemental analysis for $C_{24}H_{27}N_5 \cdot 2HCl \cdot 7/4H_2O$ Calcd.%: C, 58.83; H, 6.69; N, 14.29 Found%: C, 58.88; H, 6.51; N, 14.13
180	NMe_2	colorless crystals [hydrochloride] (MeOH) mp,205-206.5℃ Elemental analysis for $C_{25}H_{29}N_5 \cdot 2HCl \cdot 5/2H_2O$ Calcd.%: C, 58.02; H, 7.01; N, 13.53 Found%: C, 58.01; H, 7.02; N, 13.50
181		colorless crystals [hydrochloride] (EtOH) mp,210-212℃ Elemental analysis for $C_{26}H_{29}N_5 \cdot 2HCl \cdot H_2O$ Calcd.%: C, 62.15; H, 6.62; N, 13.94 Found%: C, 61.99; H, 6.44; N, 13.85



Example	R^2	Physical properties (Recrystallization solvent)
182	NHBn	colorless crystals [hydrochloride] (iso-PrOH) mp,244-245℃ Elemental analysis for $C_{30}H_{31}N_5 \cdot 2HCl \cdot 3/4H_2O$ Calcd.%: C, 65.75; H, 6.35; N, 12.78 Found%: C, 65.81; H, 6.13; N, 12.68
183		pale yellow crystals [hydrochloride] (EtOH) mp,190-193℃ Elemental analysis for $C_{29}H_{30}N_6 \cdot 3HCl \cdot 2H_2O$ Calcd.%: C, 57.29; H, 6.13; N, 13.82 Found%: C, 57.46; H, 5.98; N, 13.77
184		pale yellow crystals [hydrochloride] (EtOH) mp,231.5-232℃ Elemental analysis for $C_{28}H_{34}N_6 \cdot 3HCl \cdot 3/4H_2O$ Calcd.%: C, 58.23; H, 6.72; N, 14.55 Found%: C, 58.12; H, 6.93; N, 14.46
185		colorless needles [hydrochloride] (EtOH) mp,187-189℃ Elemental analysis for $C_{28}H_{33}N_5 \cdot 2HCl \cdot 3/4H_2O$ Calcd.%: C, 63.93; H, 6.99; N, 13.31 Found%: C, 64.05; H, 6.93; N, 13.32
186		colorless crystals [hydrochloride] (EtOH-iso-PrOH) mp,194-195℃ Elemental analysis for $C_{27}H_{31}N_5O \cdot 2HCl \cdot 3/2H_2O$ Calcd.%: C, 59.89; H, 6.70; N, 12.93 Found%: C, 59.72; H, 6.64; N, 12.85

Example 187

1-[2-(N-n-Butyl-4-piperidyl)ethyl]-4-chloro-1H-imidazo[4,5-c]quinoline hydrochloride

[0119] To a suspension of 1.20 g of 4-chloro-1-[2-(4-piperidyl)ethyl]-1H-imidazo-[4,5-c]quinoline trifluoroacetate and 0.77 g of potassium carbonate in 6 ml of N,N-dimethylformamide, 0.30 ml of n-butyl bromide was added dropwise at room temperature, and the mixture was stirred for 5 hours. The reaction mixture was adjusted to pH 10 with 10% aqueous sodium hydroxide solution, and extracted with ethyl acetate. The extract was washed successively with water and saturated brine, and dried, and then the solvent was evaporated to give 0.92 g of a pale brown liquid. The resulting liquid was dissolved in tetrahydrofuran. The solution was filtered on silica gel, and the filtrate was concentrated to give 0 87 g of a colorless solid. Hydrochloride was prepared in a conventional method. Recrystallization from a mixture of methanol and ethyl acetate gave colorless crystals having the melting point of from 144 to 158°C.

Elemental analysis for $C_{21}H_{27}ClN_4 \cdot 2HCl \cdot 1/2H_2O$			
Calculated %	C, 55.70;	H, 6.68;	N, 12.37
Found %	C, 55.80;	H, 6.65;	N, 12.44

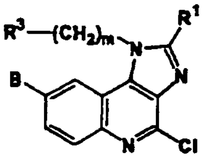
Example 188

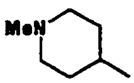
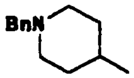
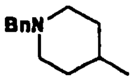
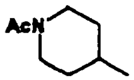
1-[2-(N-Acetyl-4-piperidyl)ethyl]-4-chloro-1H-imidazo[4,5-c]quinoline

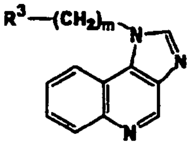
[0120] To a solution of 0.60 g of 4-chloro-1-[2-(4-piperidyl)ethyl]-1H-imidazo-[4,5-c]quinoline trifluoroacetate in 4 ml of pyridine, 2 ml of acetic anhydride was added, and the mixture was stirred at room temperature for 1 hour After the reaction, the solvent was evaporated. The residue was added with isopropanol and diisopropyl ether, and the precipitated crystals were collected by filtration, and washed with diisopropyl ether to give 0.45 g of colorless crystals. Recrystallization from a mixture of methylene chloride and diisopropyl ether gave colorless crystals having the melting point of from 183 to 186.5°C.

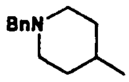
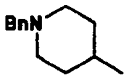
Elemental analysis for $C_{19}H_{21}ClN_4O$			
Calculated %	C, 63.95;	H, 5 93;	N, 15.70
Found %	C, 63.81;	H, 5.87;	N, 15.61

[0121] In accorcance with the methods of Examples 187 and 188, the compounds of Examples 189 through 194 were obtained.



Example	R^1	B	R^3	m	Physical properties (Recrystallization solvent)
189	Ph	H		2	colorless crystals (iso-PrOH) mp,167-168°C Elemental analysis for $C_{24}H_{25}ClN_4$ Calcd.%: C, 71.19; H, 6.22; N, 13.84 Found%: C, 71.00; H, 6.18; N, 13.56
190	H	Cl		2	colorless crystals [hydrochloride] (EtOH) mp,235-246°C (decomposition) Elemental analysis for $C_{24}H_{24}Cl_2N_4 \cdot HCl \cdot 1/4H_2O$ Calcd.%: C, 60.01; H, 5.35; N, 11.66 Found%: C, 60.01; H, 5.62; N, 11.67
191	H	H		1	colorless crystals [hydrochloride] (EtOH) mp,248-257°C (decomposition) Elemental analysis for $C_{23}H_{23}ClN_4 \cdot HCl \cdot 1/4H_2O$ Calcd.%: C, 63.96; H, 5.72; N, 12.97 Found%: C, 63.98; H, 5.80; N, 12.93
192	Ph	H		2	colorless crystals (CH_2Cl_2-iso-Pr_2O) mp,154.5-160°C Elemental analysis for $C_{25}H_{25}ClN_4O \cdot 1/8H_2O$ Calcd.%: C, 69.00; H, 5.85; N, 12.87 Found%: C, 68.78; H, 5.78; N, 12.71



Example	R^3	m	Physical properties (Recrystallization solvent)
193		1	colorless crystals [hydrochloride] (MeOH-iso-Pr_2O) mp,269-280℃(decomposition) Elemental analysis for $C_{23}H_{24}N_4 \cdot 2HCl \cdot 3/4H_2O$ Calcd.%: C, 62.37; H, 6.26; N, 12.65 Found%: C, 62.36; H, 6.45; N, 12.60
194		2	colorless crystals [hydrochloride] (MeOH-iso-Pr_2O) mp,150-156℃(decomposition) Elemental analysis for $C_{24}H_{28}N_4 \cdot 2HCl \cdot 1/2H_2O$ Calcd.%: C, 63.71; H, 6.48; N, 12.38 Found%: C, 63.90; H, 6.68; N, 12.11

Example 195

4-Chloro-1-[2-[N-(4-fluorophenylsulfonyl)-4-piperidyl]ethyl]-1H-imidazo-[4,5-c]quinoline

[0122] To a suspension of 0.50 g of 4-chloro-1-[2-(4-piperidyl)ethyl]-1H-imidazo-[4,5-c]quinoline trifluoroacetate and 0.32 g of potassium carbonate in 2 ml of N,N-dimethylformamide, a solution of 0.23 g of p-fluorobenzenesulfonyl chloride in 3 ml of N,N-dimethylformamide was added dropwise at room temperature, and the mixture was stirred for 5 hours. The reaction mixture was adjusted to pH 10 with 10% aqueous sodium hydroxide solution, and extracted with ethyl acetate. The extract was washed successively with water and saturated brine, and dried, and then the solvent was evaporated to give 0.35 g of a colorless solid. Recrystallization from a mixture of methanol, ethanol and water gave colorless crystals having the melting point of from 175 to 178.5°C.

Elemental analysis for $C_{23}H_{22}ClFN_4O_2S$			
Calculated %	C, 58.41;	H, 4.69;	N, 11.85
Found %	C, 58.43;	H, 4.52;	N, 11.88

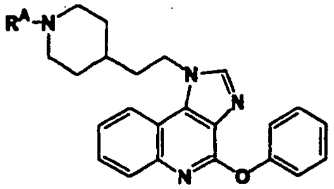
Example 196

1-[2-(N-Methanesulfonyl-4-piperidyl)ethyl]-4-phenoxy-1H-imidazo[4,5-c]-quinoline

[0123] To a solution of 1.00 g of 4-phenoxy-1-[2-(4-piperidyl)ethyl]-1H-imidazo-[4,5-c]quinoline trifluoroacetate and 0.57 ml of triethylamine in 10 ml of methylene chloride, 0.16 ml of methanesulfonyl chloride was added dropwise at room temperature, and the mixture was stirred for 1.5 hours. The reaction mixture was added with water, and extracted with methylene chloride. The extract was washed with water, and dried, and then the solvent was evaporated to give a colorless liquid. The resulting colorless liquid was solidified with ethyl acetate, and the solid was washed with diethyl ether to give 0.80 g of colorless crystals. Recrystallization from a mixture of methylene chloride and ethyl acetate gave colorless crystals having the melting point of from 173.5 to 176°C.

Elemental analysis for $C_{24}H_{26}N_4O_3S$			
Calculated %	C, 63.98;	H, 5.82;	N, 12.44
Found %	C, 64.01;	H, 5.98;	N, 12.28

[0124] In accordance with the method of Example 196, the compounds of Examples 197 through 199 were obtained.



Example	R^A	Physical properties (Recrystallization solvent)
197	Ts	colorless crystals (AcOEt-iso-Pr_2O) mp,201.5-202°C Elemental analysis for $C_{30}H_{30}N_4O_3S$ Calcd.%: C, 68.42; H, 5.74; N, 10.64 Found%: C, 68.46; H, 5.83; N, 10.53
198	EtO_2C	colorless crystals (AcOEt-iso-Pr_2O) mp,132-133°C Elemental analysis for $C_{26}H_{28}N_4O_3$ Calcd.%: C, 70.25; H, 6.35; N, 12.60 Found%: C, 70.13; H, 6.34; N, 12.50
199	BnO_2C	yellow liquid NMR spectrum δ ($CDCl_3$)ppm: 1.31 (2H,brs),1.50-1.70(1H,m),1.78(2H,brs),2.00(2H,q,J= 7.5Hz),2.81(2H,brs),4.23(2H, brs),4.63(2H,t,J=7.5Hz),5.1 3(2H,s),7.25(1H,t,J=7Hz),7.30-7.40(5H,m),7.39(2H,d,J= 7Hz), 7.44(2H,t,J=7Hz),7 50(1H,td,J=8.5,1Hz),7.57(1H,t d,J=8.5,1Hz),7 90(1H,dd,J=8.5,1Hz), 7.94(1H,s),8.04(1H, dd,J=8.5,1Hz) IR spectrum ν (liq.) cm^{-1}:1698 Mass spectrum m/z:506(M^+)

Example 200

4-[2 -(4-Amino-1H-imidazo [4,5-c]quinolin-1-yl)ethyl]-N-methyl-1-piperidine-carbothioamide

[0125] A suspension of 0.50 g of 4-amino-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]-quinoline and 0.37 g of methylisothiocyanate in 10 ml of methylene chloride was stirred at room temperature for 1 hour, and then the precipitated crystals were collected by filtration to give 0.56 g of colorless crystals. Recrystallization from a mixture of methylene chloride and methanol gave colorless crystals having the melting point of from 216 to 218°C.

Elemental analysis for $C_{19}H_{24}N_6S \cdot 1/2H_2O$			
Calculated %	C, 60.45;	H, 6.67;	N, 22.26
Found %	C, 60.79;	H, 6.66;	N, 21.97

[0126] In accordance with the method of Example 200, the compound of Example 201 was obtained.

Example 201

4-[2-(4-Chloro-2-phenyl-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]-N-methyl-1-piperidinecarbothioamide

[0127]

Appearance: colorless crystals
Recrystallization solvent: methanol
mp: 215-220°C (decomposition)

Elemental analysis for $C_{25}H_{26}ClN_5S$			
Calculated %	C, 64.71;	H, 5.65;	N, 15.09
Found %	C, 64 80;	H, 5.62;	N, 14.96

Example 202

1-[2 -(1-Amidino-4-piperidyl)ethyl]-4-chloro-2-phenyl-1H-imidazo[4,5-c]-quinoline hydrochloride

[0128] A solution of 0.75 g of 4-chloro-2-phenyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo-[4,5-c]quinoline, 0.40 g of 1H-pyrazole-1-carboxyamidine hydrochloride and 0.39 ml of triethylamine in 5 ml of N,N-dimethylformamide was stirred at room temperature for 19 hours The reaction solution was concentrated and the residue was added with ethanol, and then the precipitated crystals were collected by filtration to give 0.51 g of colorless crystals. Recrystallization from ethanol gave colorless crystals having the melting point of from 270 to 273°C (decomposition).

Elemental analysis for $C_{24}H_{25}ClN_6 \cdot HCl \cdot 1/2H_2O$			
Calculated %	C, 60.25;	H, 5.69;	N, 17.57
Found %	C, 60.47;	H, 5.61;	N, 17.36

[0129] As an example of the excellent effects of the compounds according to the present invention, experimental results of inhibitory actions against production of TNF- α and IL-1β in human cells will be shown below

1. Preparation of blood cells for culture

[0130] About 50 mL of whole blood was collected from adult healthy volunteers by venepuncture into a plastic tube which containing 170 μL of Novo-heparin 1000 (Novo-Nordisk A/S). Then, PBMCs (Peripheral Blood Mononuclear Cells) were prepared using a cell separation tube, LeucoPREP™ (Becton Dickinson), and cultured with RPMI-1840 medium (Nissui Pharmaceutical Co.) containing 2 mM L -glutamine (Life Technologies), 2.5 U/ml penicillin-2.5 μg/mL streptomycin solution (Life Technologies) supplemented with 10% fetal calf serum (Intergen Company) at $1x10^6$ cells/mL.

2. Preparation of test compounds

[0131] Test compounds were dissolved in distilled ultra-pure water, dimethyl sulfoxide, or 0.1 N hydrochloric acid at 20 μM, and then sequentially diluted with saline and used. The compounds were examined at concentrations ranging from 10^{-10} M to 10^{-5} M.

3. Treatment of cells with medicaments

[0132] 10 μL of 1 μg/mL lipopolysaccharide (LPS) was added to a 96-well (flat bottom) plate for cell culture, MicroTest III ™ tissue culture plate (Becton Dickinson), containing 180 μL of the PBMCs in the aforementioned medium. After 30 minutes, 10 μL of the solution of the test compound or the solvent was further added to each well, and the plate was covered with a plastic lid and incubated at 37°C for 16 hours in an atmosphere of 5% CO_2.

4. Determination of human TNF-a and human IL-1β

[0133] An enzyme immunoassay by the sandwich method was performed to determine the human TNF- α and human IL-1β in the culture supernatant. The anti-cytokine antibody (the first-antibody) was diluted and placed in a 96-well microtiter plates for coating. After the wells were washed, the culture supernatant was appropriately diluted, and then added to each well and incubated. Then the second-antibody against cytokine and the third-antibody against the second-antibody were successively added while applying washing processes between the operations. After the final washing process, a tetramethylbenzidine solution (DAKO) was added to each well to start the coloring reaction. The coloring reaction was quenched with 1 N sulfuric acid, and then the absorbance at 450 nm of each well was measured by a microplate reader, M-Vmax™ (Molecular Devices). The concentrations of the cytokines were determined by quantification software, Softmax™ (Molecular Devices), in comparison with the calibration curves obtained by using the recombinant cytokines as the standards. For determination of human TNF-α, monoclonal anti-human TNF-α (ENDOGEN), polyclonal rabbit anti-human TNF-α (Pharma Biotechnologie Hannover), peroxidase conjugated donkey anti-rabbit IgG (Jackson ImmunoRes. Labs.), and recombinant human TNF-α (INTERGEN Company) were used for the first-, second- and third-antibodys and the standard for the calibration curve, respectively. For determination of human IL-1β, monoclonal anti-human IL-1β (Cistron), polyclonal sheep anti-human IL-1β (Biogenesis), HRP conjugated donkey anti-goat IgG (Chemicon International), and recombinant human IL-1β (R&D Systems) were used for the first-, second- and third-antibodys and the standard for the calibration curve, respectively.

[0134] In both cases for TNF- α and IL-1 β, the activities of each test compound are shown as percentages (%) of the amount of the cytokine induced by treatment with LPS together with the test compound against the amount of the cytokine induced by treatment solely with LPS

[0135] Results are shown in tables 1 and 2.

Table 1:

Inhibitory action against TNF- α production in human cells					
Compounds	Administered concentration (μmol/L)				
	0.001	0 01	0.10	1.0	10
Example 89	91	86	90	84	17
Example 110	80	77	26	1	0
Example 113	68	81	86	69	29
Example 117	117	77	71	24	0
Example 118	79	91	88	51	3
Example 121	81	91	49	0	0

Table 2:

Inhibitory action against IL-1 β production in human cells					
Compounds	Administered concentration (μmol/L)				
	0.001	0.01	0.10	1.0	10
Example 89	112	102	96	63	0
Example 110	119	105	85	64	14
Example 113	104	109	116	96	30
Example 117	119	106	111	72	8
Example 118	96	106	102	59	0
Example 121	102	108	87	24	0

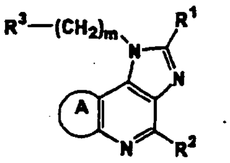
[0136] These results clearly indicate that the compounds of the present invention have excellent inhibitory actions against production of TNF and IL-1.

Industrial Applicability

[0137] The compounds of the present invention have excellent inhibitory actions against production of TNF or IL-1 and are extreamely useful as preventive or therapeutic agents of diseases mediated by these cytokines.

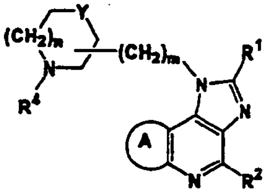
Claims

1. A 1H-imidazopyridine derivative represented by the following general formula or a salt thereof:



wherein R^1 represents hydrogen atom, hydroxyl group, an alkyl group which may have one or more substituents, a cycloalkyl group which may be substituted, a styryl group which may be substituted, or an aryl group which may have one or more substitutents; R^2 represents hydrogen atom, an alkyl group, a halogen atom, hydroxyl group, an amino group which may have one or two substituents, a cyclic amino group which may be substituted, or a phenoxy group which may be substituted; ring A represents a homocyclic or a heterocyclic ring which may be substituted with one or more alkyl groups, alkoxyl groups, or halogen atoms; R^3 represents a saturated nitrogen-containing heterocyclic group which may be substituted; and m represents an integer of from 0 to 3; provided when R^3 represents unsubstituted piperidino group, at least one of R^1 and R^2 is not hydrogen atom.

2. A 1H-imidazopyridine derivative represented by the following general formula or a salt thereof:



wherein R^1 represents hydrogen atom, hydroxyl group, an alkyl group which may have one or more substituents, a cycloalkyl group which may be substituted, a styryl group which may be substituted, or an aryl group which may have one or more substitutents; R^2 represents hydrogen atom, an alkyl group, a halogen atom, hydroxyl group, an amino group which may have one or two substituents, a cyclic amino group which may be substituted, or a phenoxy group which may be substituted; ring A represents a homocyclic or heterocyclic ring which may be substituted with one or more alkyl groups, alkoxyl groups, or halogen atoms; m represents an integer of from 0 to 3; R^4 represents hydrogen atom, an alkyl group, benzyl group, triphenylmethyl group, an alkanoyl group which may be substituted, an alkoxycarbonyl group, benzyloxycarbonyl group, a thiocarbamoyl group which may be substituted, an alkanesulfonyl group, a benzenesulfonyl group which may be substituted, or amidino group; Y represents methylene group, oxygen atom, sulfur atom, nitrogen atom, a group represented by NH, or a single bond; and n represents an integer of from 0 to 2.

3. The compound or the salt thereof according to claim 1 or claim 2, wherein the ring A is benzene ring or thiophene ring.

4. A medicament which comprises as an active ingredient the 1H-imidazopyridine derivative or a pharmacologically acceptable salt thereof according to claim 1 or claim 2.

5. The medicament according to claim 4 which is used for preventive or therapeutic treatment of a disease in which a cytokine is mediated.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP99/04381

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl^6 C07D471/04, C07D471/14, C07D491/113, C07D495/14, A61K31/435, A61K31/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int. Cl^6 C07D471/04, C07D471/14, C07D491/113, C07D495/14, A61K31/435, A61K31/47

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS, REGISTRY(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO, 9830562, A (Terumo Kabushiki Kaisha), 16 July, 1998 (16.07.98), & EP, 894797, A	1-5
A	JP, 09208584, A (Terumo Kabushiki Kaisha), 12 August, 1997 (12.08.97), (Family: none)	1-5
A	US, 5389640, A (Minnesota Mining and MFG. Co.), 14 February, 1995 (14.02.95), & EP, 872478, A	1-5
A	US, 5352784, A (Minnesota Mining and MFG. Co.), 04 October, 1994 (04.10.94), & EP, 708773, A & JP, 09500628, A	1-5
A	J. Interferon Res. (1994), 14, P. 81-85	1-5
A	EP, 459505, A (Kyowa Hakko Kogyo Co., Ltd.), 04. December, 1991 (04.12.91), & JP, 04226985, A	1-5

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
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Date of the actual completion of the international search 08 November, 1999 (08.11.99)	Date of mailing of the international search report 16 November, 1999 (16.11.99)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP99/04381

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, 4689338, A (Riker Laboratories, Inc.), 16 July, 1998 (16.07.98), (Family: none)	1-5
A	EP, 145340, A (Riker Laboratories, Inc.), 19 June, 1985 (19.06.85), & JP, 60123488, A & US, 4698348, A	1-5
A	HU, 34479, A (Egypt Gyogyszervegyeszeti Gyar), 28 March, 1985 (28.03.85), (Family: none)	1-5
A	J. Med. Chem. (1968), 11(1), P. 87-92	1-5

Form PCT/ISA/210 (continuation of second sheet) (July 1992)